Neurology

OFFICIAL JOURNAL OF
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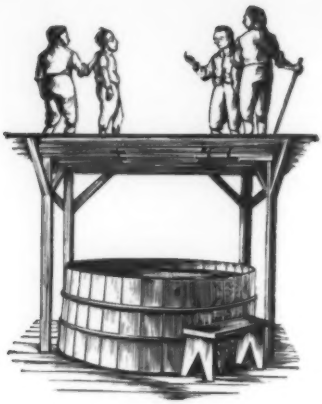
JUNE--1959

Volume 9 - Number 6



"Surprise Bath" used in colonial times to "restore the distracted to their senses." Original wood engraving by John De Pol.

to restore them to th

Less than 200 years ago, the mentally ill were bled, purged, beaten and sometimes nearly drowned in efforts to restore them to their senses.

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their senses

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*W.A. Leff, *Antibiotic Med. & Clin. Therapy*, 6: (Suppl. 1), 44-48, Feb. 1959.

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*Livingston, S., and Petersen, D.: New England J. Med. 254:327 (Feb. 16) 1956.

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INFORMATION FOR *Authors*

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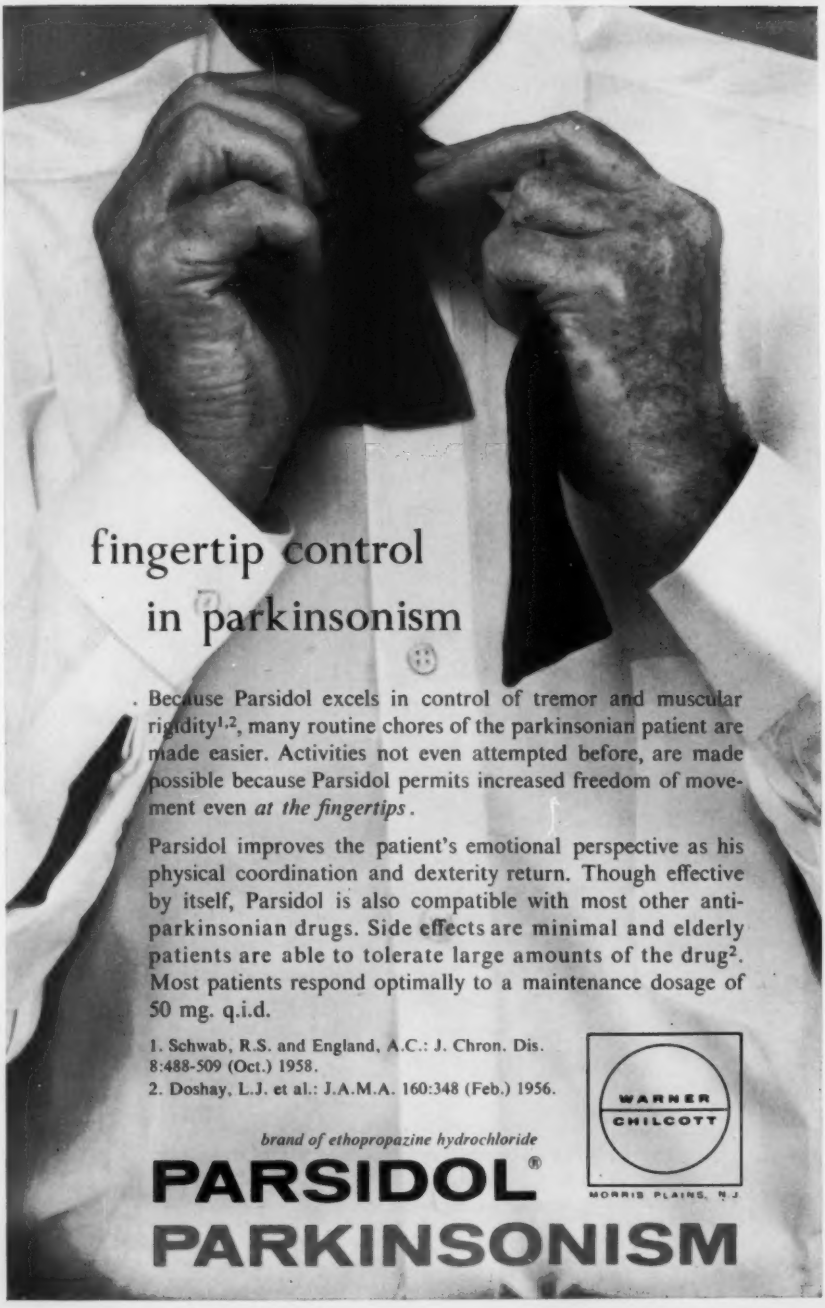
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1. Schwab, R.S. and England, A.C.: J. Chron. Dis. 8:488-509 (Oct.) 1958.
2. Doshay, L.J. et al.: J.A.M.A. 160:348 (Feb.) 1956.
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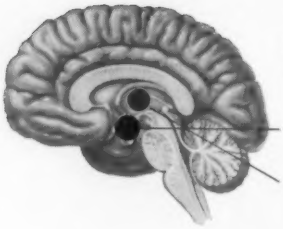

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1. Rinaldi, F., and Himwich, M.E.: Dis. Nerv. System *16*:133-141 (May) 1955.
2. Berger, F.M.: J. Pharmacol. & Exper. Therap. *112*:413-423 (Dec.) 1954.
3. Ehrmantraut, W., et al.: Presented as a Scientific Exhibit, District of Columbia Medical Society Convention, Nov. 24-26, 1958.
4. Parks, R.V.: Internat. Rec. M. *171*:678-683 (Nov.) 1958.
5. Case reports on file at Wyeth Laboratories.

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*Carter, S.: *M. Clin. North America:* 315 (March) 1953.

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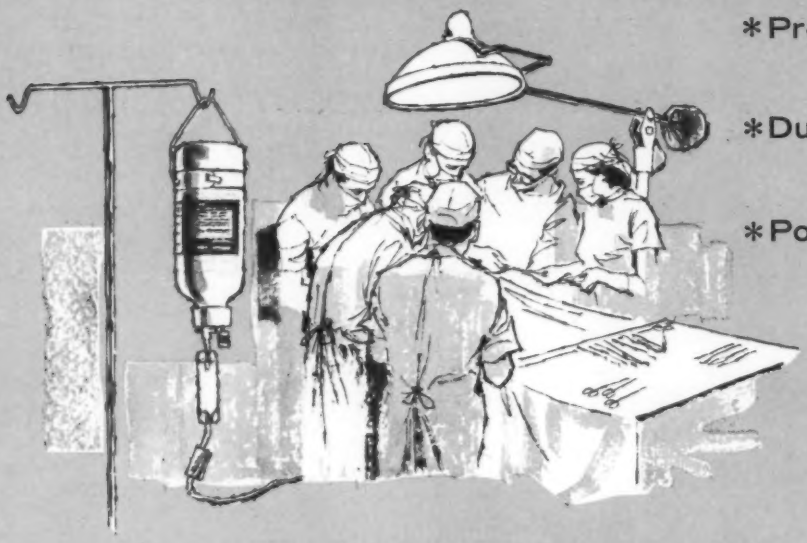

*Preoperatively

*During Surgery

*Postoperatively

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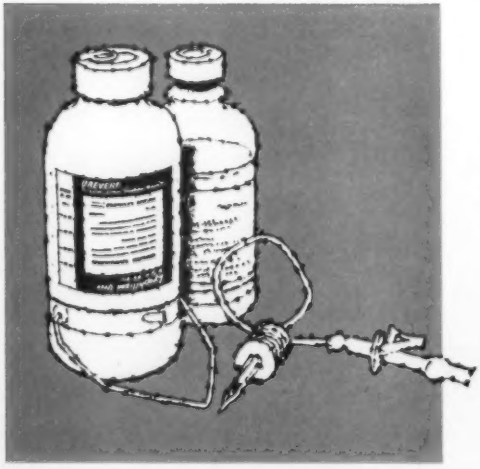

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†Javid, M.: Urea – New Use of an Old Agent, Reduction of Intracranial a Intraocular Pressure, The Surgical Clinics of North America, Philadelph W. B. Saunders Company, August, 1958, p. 907.

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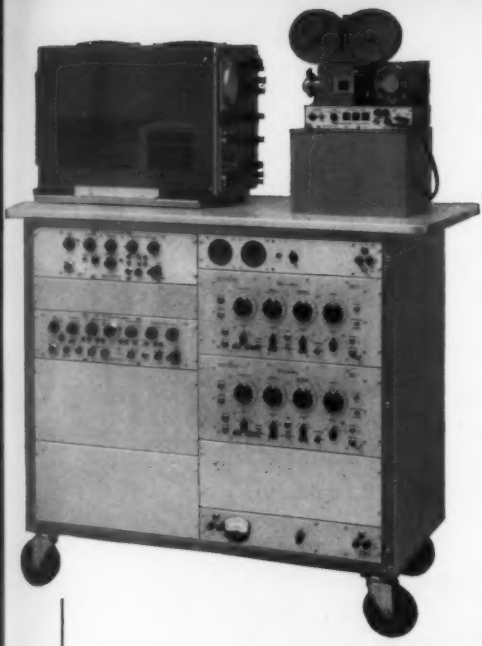

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1. Mitchell, E.H.: M. Ann. District of Columbia *27*:1 (April) 1958. 2. Cooper, C.D., and Epstein, J.H.: Am. M. Sc. *235*:448 (April) 1958. 3. Vazuka, F.A.: Neurolog *8*:446 (June) 1958. 4. Cobey, M.C.: Am. Surgeon *24*:3 (April) 1958. 5, 6. Wein, A.B.: M. Ann. District of C lumbia *27*:346 (July) 1958; Clin. Med. *6*:44 (Jan.) 19

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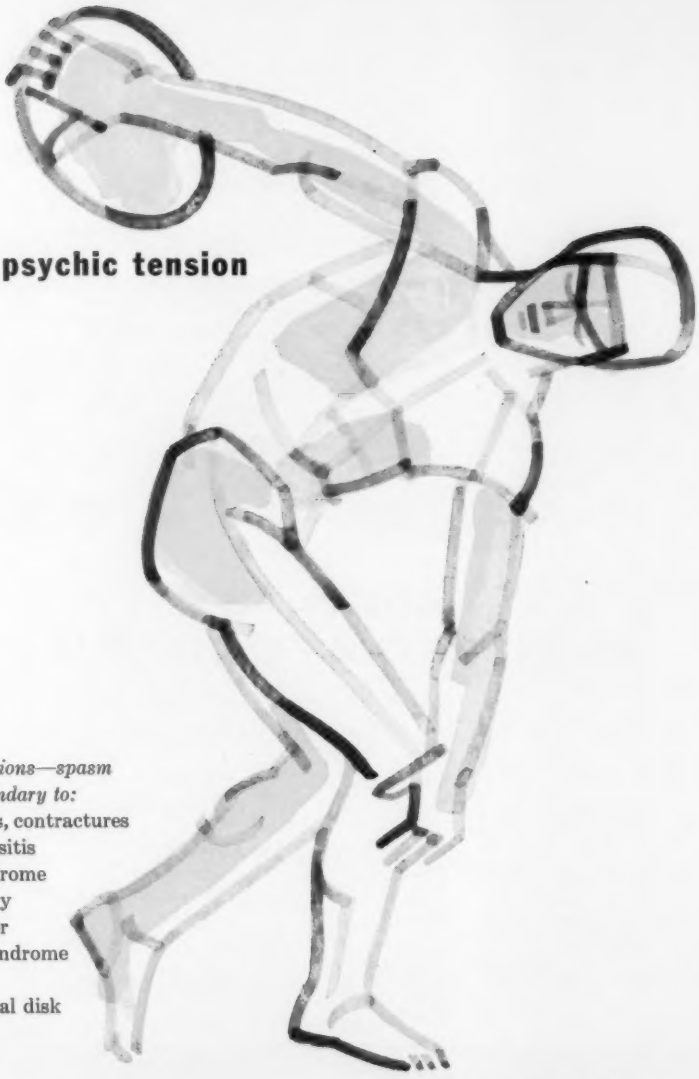

Partial indications—spasm or tension secondary to:
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- fibrositis, myositis
- low-back syndrome
- whiplash injury
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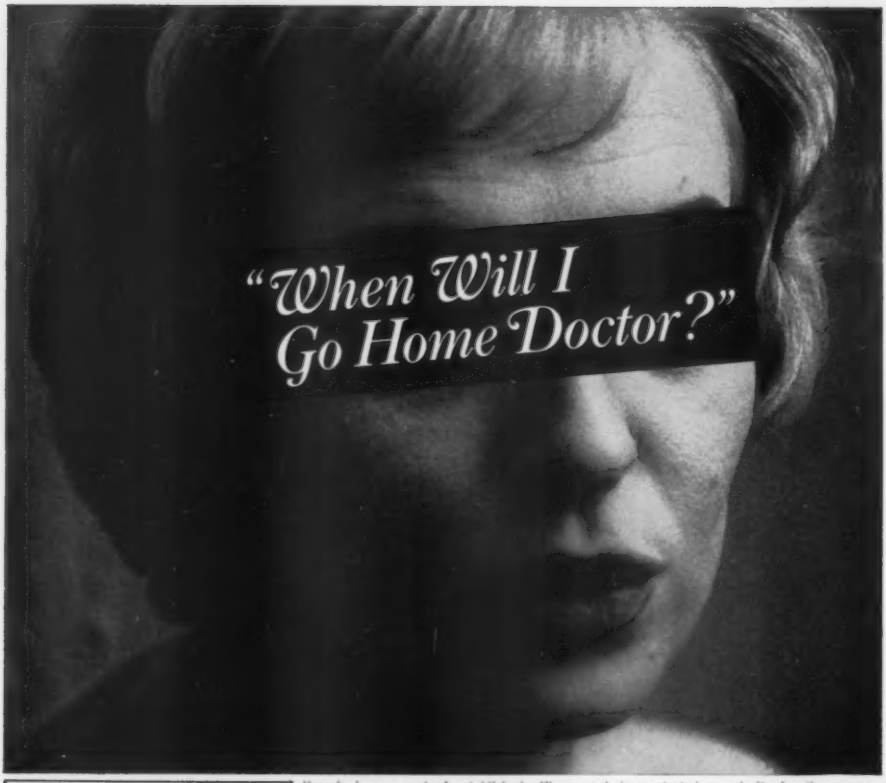

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Study of lipids in cerebrospinal fluid

VI. The normal lipid profile

Wallace W. Tourtellotte, Ph.D., M.D.

THIS REPORT PRESENTS the normal lipid profile of cerebrospinal fluid. New information about the concentration of the various lipids in normal fluid is being used as a basis for study of possible abnormalities of spinal fluid lipids in patients with multiple sclerosis.

A summary of the concentration of various lipids in normal fluid discussed in the literature appears in table 1.[1] The observed total phospholipid averaged about 0.6 mg. per 100 cc. (per cent) of cerebrospinal fluid. A search for the determination of particular phospholipids—such as various cephalins, lecithin, sphingomyelin, and diphosphoinositide—revealed that only one of the cephalins, plasmalogen, had been quantitated. Average concentration reported was 0.3 mg. per cent. The cerebroside values were found unreasonable; one investigator found more cerebroside in spinal fluid than the amount of total lipid in the serum (700 mg. per cent).

The values given by many recent investigators indicate that total cholesterol falls in a rather narrow range, 0.1 to 0.5 mg. per cent. Free cholesterol has not been detected in normal fluids. Only a few have attempted to determine total lipid; range was 0.5 to 3.7 mg. per cent.

Finally, because no one investigator had determined the total lipid, total phospholipid, total cholesterol, and cerebroside concentration on a single spinal fluid specimen, the neutral fat content could not be calculated. From this recent, exhaustive review of the literature, apparently the lipid chemistry of the spinal fluid was almost unknown, although not unexplored.[1] Standardized ultramicrochemical technics have to be applied to normal and abnormal fluids if neurochemical correlations are to be made.

Since the chemistry of the lipids in the cerebrospinal fluid is not known at the present time, the terminology used by Rossiter for lipids in the central nervous system has been adopted for this report; further study will probably show similar compounds in the spinal fluid.[2] The lipids are divided into the following great groups: (1) phospholipids (phosphatide) or lipids containing phosphorus, which include phosphoglycerides (cephalins

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A preliminary report of this study was presented at the Ninth Annual Meeting of the American Academy of Neurology, April 26, 1957, and in the Transactions of the American Neurological Association 83:132, 1958.

TABLE 1
THE CONCENTRATION OF VARIOUS LIPID FRACTIONS IN NORMAL CEREBROSPINAL FLUID

Lipid	*Milligram per 100 cc. of Cerebrospinal Fluid* Literature (Selected authors)	*Our data*
Observed total phospholipid	0.6	0.370
Cephalins	0.3 (plasmalogens)	0.090 (total)
Lecithin	Not done	0.168
Sphingomyelin	Not done	0.087
Diphosphoinositide	Not done	Not done
Cerebroside	3 to 700	0.059
Total cholesterol	0.1 to 0.5	0.415
Free cholesterol	Not done	0.109
Observed total lipid	0.5 to 3.7	1.254
Calculated neutral fat (Unaccounted for lipids)	Not available	0.409

and lecithin), phosphoinositide, and phosphosphingoside (sphingomyelin); (2) glycolipids or lipids that contain a carbohydrate group, which include cerebroside, ganglioside, and strandin; (3) sterols such as cholesterol and cholesterol ester which is not found in normal brain; and (4) neutral fat or triglycerides, although not found in normal brain.

The data which are presented here on the lipids in the normal spinal fluid are only as good as the methods used to obtain them. Our previous reports dealt in detail with the limitations and standardization of the most reliable ultramicrolipid technics now available.[3–6]

In addition to tests of the method, we have standardized an ultramicrocholine procedure[7] and demonstrated the presence of choline in the aqueous phase (the mild potassium hydroxide decomposable phospholipids of Brante[8]) and in the hexanol phase (sphingolipid fraction). The application of this procedure to spinal fluid (pneumoencephalographic fluid) yielded a lipid choline to lipid phosphorus ratio in the aqueous phase (cephalins + lecithin + diphosphoinositide) and hexanol phase (sphingolipids) of 1.02 and 1.06, respectively. These ratios of choline to phosphorus of about 1 to 1 are as predicted by the elemental structure of lecithin and sphingomyelin. These combined choline and phosphorus experiments leave little doubt that phospholipids, such as classic lecithin and sphingomyelin, are present in spinal fluid.

Further proof that the proposed methods standardized for the spinal fluid are determining the various lipids properly rests upon an experiment in which the proposed methods for the spinal fluid were applied to 21 normal fasting serums. Data agreed well with normal values obtained by very different methods.[9]

Another argument for the reliability of the procedures is shown in table 2. The average calculated phospholipid shown in column 5 and the observed total phospholipid shown in column 6 are not significantly different. The average calculated phospholipid is obtained by adding columns 1, 2, and 3. This value is 466 μM. per cent. The observed total phospholipid value was obtained by analyzing another portion of the lipid extract. The value obtained on the average was 501 μM. per cent. Average recovery of 94%, as shown in column 7, indicated that no significant loss of the phospholipid phosphorus occurred in the separation into phosphoglycerides (cephalins and lecithins) and phosphosphingoside (sphingomyelin) and, further, that this microanalysis was not contaminated. The sensitivity of the phosphorus procedure used was 0.003 μg.[4]

METHODS

Lumbar cerebrospinal fluid was removed from 9 women and 19 men. None of the sub-

TABLE 2

THE CONCENTRATION OF VARIOUS LIPIDS IN NORMAL NONFASTING CEREBROSPINAL FLUID

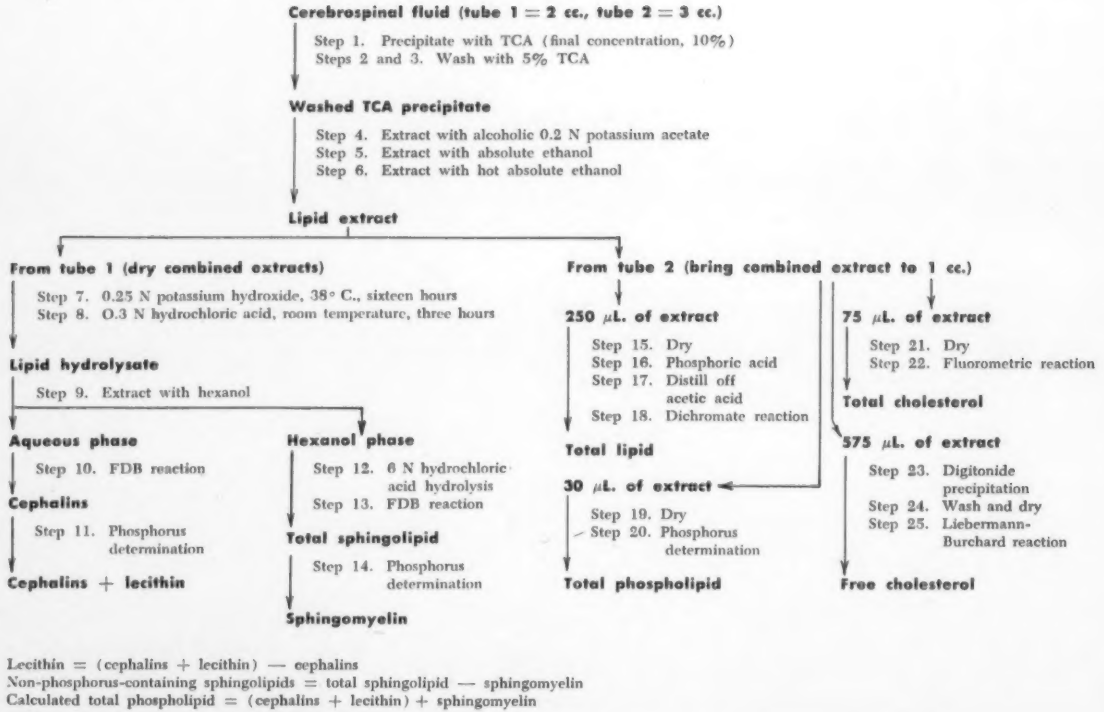
	Cephalins mμM. per cent 1	*Calculated lecithin* mμM. per cent 2	*Sphingomyelin phosphorus* mμM. per cent 3	*Calculated nonphosphorus-containing sphingolipids* mμM. per cent 4	*Calculated total phospholipid* mμM. per cent 5	*Observed total phospholipid* mμM. per cent 6	*Per cent recovery phospholipid* μg. per cent 7	*Total cholesterol* μg. per cent 8	*Free cholesterol* μg. per cent 9	*Per cent free cholesterol* μg. per cent 10	*Observed total lipid* μg. per cent 11
Men and Women											
Number of determinations	27	27	27	24	27	23	23	27	23	23	23
Mean	128	224	116	73	466	301	94	415	109	28	1254
s.e.m.	5.2	10.1	6.1	8.1	15.6	15.6		17.6	4.7	1.1	56.7
Range	79 to 173	104 to 383	79 to 211	0 to 141	339 to 642	381 to 621	79 to 112	264 to 520	72 to 145	16 to 39	544 to 1668
Men											
Number of determinations	18		18			17				14	17
Mean	127		127			526				26	1351
s.e.m.	7.69		7.69			15.2				1.03	43.3
Range	83 to 211		83 to 211			439 to 621				16 to 32	921 to 1668
Women											
Number of determinations	9		9			6				9	6
Mean	95		95			433				31	980
s.e.m.	2.54		2.54			24.9				.7	95.6
Range	79 to 114		79 to 114			381 to 515				22 to 39	544 to 1196

mμM. per cent indicates millimicromole (1,000 × micromol) per 100 cc. of spinal fluid.

jects had had any detectable neurologic, surgical, or medical disease. They had eaten one to three hours before lumbar puncture. Average age of the women was 21.3 years; average age of the men was 27.1 years. Since multiple sclerosis most frequently attacks the young adult, this age group (20 to 34 years) serves well as the norm for future studies.

After establishing the spinal fluid pressure by a glass manometer, the fluid was collected serially in 3 separate tubes: 1 cc., 15 cc., and 1 cc. Cell counts were done on tubes 1 and 3. Tube 2 was immediately centrifuged for twenty minutes at 1,100 R.C.F. (relative centrifugal force), at a radial distance of 25 cm. at 4° C. The cell-free supernate was carefully removed and 4 cc. used for the micro-Kahn reaction for syphilis, sulfosalicylic acid test of total protein, and the qualitative zinc sulfate reaction for globulin. The protein was also determined by several different protein procedures recently standardized in this laboratory.[10,11]

Only 1 subject had a spinal fluid pressure over 200 mm. of water. The initial and final pressures were 240 and 220 mm., respectively. Because the lipid values in the spinal fluid of this subject did not differ from values obtained on the other subjects considered healthy, these data were not discarded. On the other hand, the specimen from 1 subject was discarded because his total protein was 60.3 mg. per 100 cc. and the fluid had a significant red blood cell contamination. The white blood cell count on all the spinal fluids averaged 2.3 mononuclear cells per cubic millimeter. The spinal


Cerebrospinal fluid (tube 1 = 2 cc., tube 2 = 3 cc.)
Step 1. Precipitate with TCA (final concentration, 10%)
Steps 2 and 3. Wash with 5% TCA
Washed TCA precipitate
Step 4. Extract with alcoholic 0.2 N potassium acetate
Step 5. Extract with absolute ethanol
Step 6. Extract with hot absolute ethanol
Lipid extract
From tube 1 (dry combined extracts)
Step 7. 0.25 N potassium hydroxide, 38° C., sixteen hours
Step 8. 0.3 N hydrochloric acid, room temperature, three hours
Lipid hydrolysate
Step 9. Extract with hexanol
Aqueous phase
Step 10. FDB reaction
Cephalins
Step 11. Phosphorus determination
Cephalins + lecithin
Hexanol phase
Step 12. 6 N hydrochloric acid hydrolysis
Step 13. FDB reaction
Total sphingolipid
Step 14. Phosphorus determination
Sphingomyelin
From tube 2 (bring combined extract to 1 cc.)
250 μL. of extract
Step 15. Dry
Step 16. Phosphoric acid
Step 17. Distill off acetic acid
Step 18. Dichromate reaction
Total lipid
30 μL. of extract
Step 19. Dry
Step 20. Phosphorus determination
Total phospholipid
75 μL. of extract
Step 21. Dry
Step 22. Fluorometric reaction
Total cholesterol
575 μL. of extract
Step 23. Digitonide precipitation
Step 24. Wash and dry
Step 25. Liebermann-Burchard reaction
Free cholesterol

Lecithin = (cephalins + lecithin) — cephalins
Non-phosphorus-containing sphingolipids = total sphingolipid — sphingomyelin
Calculated total phospholipid = (cephalins + lecithin) + sphingomyelin

Fig. 1. The flow diagram of the lipid analysis: 8 lipid fractions are directly determined—cephalins plus lecithin, cephalins, total sphingolipid, sphingomyelin, total lipid, total phospholipid, total cholesterol, and free cholesterol. Lecithin, nonphosphorus-containing sphingolipids, sphingomyelin, and cholesterol ester can be calculated by difference and total phospholipid and total lipid by summation.

fluid microKahn was negative in 23 subjects and was not done in 4 subjects who had negative blood serology and no clinical evidence of syphilis.

The qualitative zinc sulfate test for globulin was negative in 22 spinal fluids and was not done in 5. The subject who had 60.3 mg. per cent total protein had a trace of globulin. The total protein done by an ultramicroKjeldahl nitrogen procedure averaged 29.2 mg. per cent.[10] Postspinal puncture syndrome of headache, nausea, and vomiting was relieved by recumbency in over 50 per cent of the subjects. Possibly, this high incidence was related to the 17 cc. of spinal fluid which was removed.

The remaining spinal fluid, 10 to 11 cc., was pipetted for the lipid analysis as follows: 2 tubes, each containing 2 cc., labeled tube 1; and 2 tubes, each containing 3 cc., labeled tube 2.

The analytic scheme for the various lipids is presented in Figure 1. The lipids were extracted from trichloroacetic acid precipitated protein with buffered ethanol in steps 1 through 6. The lipid extract from tube 1 was dried; that from tube 2 was brought to a volume of 1 cc. The dried lipid extract from tube 1 was partitioned as shown in steps 7 through 14 into cephalins, cephalins plus lecithin, and total sphingolipid and sphingomyelin after the method of Robins and associates,[12] modified for spinal fluid.[6] Aliquots of the lipid extract in tube 2 were taken to determine the following: total lipids (steps 15 through 18) were determined spectrophotometrically as suggested by Bragdon,[13] modified for spinal fluid;[3] total phospholipid (steps 19 and 20), by the procedure of Lowry and associates,[14] modified for spinal fluid;[4] total cholesterol (steps 21 and 22) by the fluorometric method of Albers and Lowry,[15] modified for spinal fluid;[5] and free cholesterol (steps 23 through 25) by the method of Sperry and Webb,[16] modified for spinal fluid.[5]

The statistical analysis consisted of calculating the mean and the standard error of the mean (s.e.m) of each lipid concentration for each group—men and women, men, and women.[17] The small size of the group was taken into account by increasing the s.e.m. by the factor of $\sqrt{N(N-1)}$. The number of determinations and range are also given.

The use of millimicromoles ($m\mu M.$) per 100 cc. of spinal fluid is a better expression of the data than microgram per cent for cephalins, lecithin, sphingomyelin, cerebroside, and total phospholipid. Since 1 free amino group exists after strong acid hydrolysis in each of the various cephalins, except diphosphoinositide, and each sphingolipid molecule, and 1 phosphorus atom is found in lecithin and sphingomyelin, moles of amine and phosphorus found are direct measures of the moles of the parent compound. The various molecular weights of these complex compounds need not be considered. However, to calculate the total lipid, the phospholipid and cerebroside were converted to microgram per cent; we used an average molecular weight of 738 for the phospholipid and 810 for the cerebroside.[8] Addition of the total observed phospholipid, cerebroside, and total cholesterol, all in microgram per cent, gives the calculated total lipid not shown in table 2.

RESULTS

Table 2 summarizes the concentration of the various lipids in cerebrospinal fluid from normal individuals.

The number of determinations for the various lipid fractions does not always correspond to the number of volunteers (27). In 3 instances, the wrong reagents were added and, therefore, the nonphosphorus containing sphingolipids (column 4) could not be calculated. Also 4 determinations for total phospholipid (column 6) and total lipid were discarded because blank values were too high, indicating the presence of a contaminant. Each of 4 free cholesterol values (column 9) was discarded because the amount of sample used for analysis was not large enough for a significant colorimetric reaction. Column 11 shows that the lowest value obtained was 544 μg. per cent. This value was double checked. The next lowest value was 921 μg. per cent.

In column 5 of the table is shown the calculated phospholipid, 466 $m\mu M.$ per cent, obtained by addition of the means in columns 1, 2, and 3 ($128 + 224 + 116 = 468$). The difference between 466 and 468 is not significant but shows the effect of converting the results

to 3 significant places. In column 6 is shown the observed phospholipid, 501 mμM. per cent, obtained by analyzing a different aliquot of the lipid extract. As a check on the analysis, the percentage recovery was calculated in the usual way:

$$\frac{\text{calculated total phospholipid} \times 100}{\text{observed total phospholipid}}$$

In these experiments, the average recovery of phosphorus was 94% (column 7).

The phospholipids in the spinal fluid consist of all 3 main types: cephalins (column 1), lecithin (column 2), and sphingomyelin (column 3). Only 27.5% of the calculated total phospholipid for all the volunteers contained free amino groups and could be considered part of the cephalin fraction. These data indicate that 72.6% of the spinal fluid lipids are of the choline-containing type (calculated lecithin plus sphingomyelin phosphorus). The proportion of lecithin : cephalins : sphingomyelin was found to be 47.8 : 27.3 : 24.8.

The cerebrosides (calculated nonphosphorus containing sphingolipids) (column 4) are another group of conjugate lipids present in the spinal fluid. The mean value found was 73 mμM. per cent, or 4.7% of the observed total spinal fluid lipid.

Cholesterol is present in the spinal fluid in the form of the free unesterified alcohol and as the fatty acid ester, in the amount of 109 and 306 μg. per cent, respectively. Cholesterol esters account for about 72% of the total cholesterol in the spinal fluid of man.

The mean observed total lipids for all the volunteers was 1,254 μg. per cent. The calculated total lipids (total phospholipid + total cholesterol + cerebroside) were 845 μg. per cent with an s.e.m. ± 31.4. The unaccounted for lipid was 409 ± 52.5 μg. per cent (1254—845). No experiments have been designed to characterize the lipids in this fraction, but, classically, some of this fraction should be neutral fat.

The student t test for significance of difference between the mean for men and the mean for women was calculated. The P value or level of significance was obtained from a table of t after degrees of freedom were calculated. The level of significance (P) of 0.05 was chosen to indicate a significant difference; 1 possibility in 20 exists that the difference in the mean of the 2 groups would occur by chance alone. In table 2 we have presented the mean and s.e.m. for all subjects; (men + women) and the men and the women, only if they differed. Sphingomyelin phosphorus on the average was significantly different for men and women, 127 and 95 mμM. per cent, respectively, as was the observed total phospholipid, 526 and 433 mμM. per cent. The per cent free cholesterol differed significantly by the above criteria, namely, 26 and 31% for men and women, respectively. The men had significantly more total lipids than the women —1,351 μg. per cent compared to 980. No experiments were designed to study these differences between men and women.

DISCUSSION

These data indicate that there are lipids in the normal spinal fluid, thus confirming the observations of others.[1] In the right hand column of table 1, our data have been expressed in milligrams per 100 cc. (per cent) for comparison with values found in the literature. Seuberling[18] and Roeder,[19] employing a different solvent, established that the normal lumbar fluid contained 0.625 mg. per cent of phospholipids. Our data indicate that the quantity of phospholipid in spinal fluid is small, 0.37 mg. per cent (501 mμM. per cent × 0.738, the average phospholipid molecular weight), and that the amount is lower than the most reliable figures given in the literature. We may have found a lower value because we made a special effort to rid the lipid extract of inorganic phosphorus.[6] In spinal fluid, there is 75 times more inorganic phosphorus than phospholipid phosphorus and the lipid extract can easily be contaminated to give a falsely high phospholipid value.

Some work has been done on the partition of phospholipids in spinal fluid into various lipid entities. Specifically plasmalogens have been reported in a concentration of 0.3 mg. per cent.[1] The values given for women were significantly higher. In the proposed analysis, plasmalogens as well as other noncholine containing glycerophospholipids should appear in the cephalin fraction. The value obtained by us for cephalins was much lower, 0.091 mg. per cent. Further experimentation will be needed to establish this obvious contradiction.

Inositol has been detected in spinal fluid.[1] Only 6 per cent of the total inositol was combined, 0.162 mg. per cent. The combined inositol was not analyzed further, so the possibility exists that some may be diphosphoinositides. Only qualitative studies have been done on choline in spinal fluid.[1] Lafontaine,[20] using the Tannhauser method, found no sphingomyelin in normal spinal fluid. Future experiments will have to establish the ratio of the various cephalins (phosphatidyl ethanolamine, phosphotidyl serine, and plasmalogens) and presence of phosphoinositide in the lecithin fraction, and the possibility that the sphingomyelin fraction may contain cephalin B.[21]

Several previous investigators attempted to establish the cerebroside concentration of spinal fluid;[1] in our analysis, this fraction is most properly called nonphosphorus containing sphingolipids. Their values for normal spinal fluid were unreasonable compared to the present results. The values ranged from 3 to 5 to 700 to 800 mg. of cerebrosides per cent for 2 different investigations. Even the lowest values are 2½ times the total lipid value found by us, and the highest value is higher than the normal total lipid in blood.[9,22]

The average total cholesterol value found by us, 0.415 mg. per cent, indicates that the quantity is small but is in the range previously presented by investigators who employed reliable technics (0.1 to 0.5 mg. per cent).

To our knowledge, free cholesterol has not been previously reported in normal spinal fluid. However, its presence can be inferred from the data presented by Selbache and Trappe, who were able to separate total cholesterol in spinal fluid from neurologically ill patients into free and esterified forms; obviously, 2 forms of cholesterol would eventually be reported in spinal fluid of normal patients.[23] The data presented here show that 28% of the total cholesterol in normal spinal fluid is free. Poser and Curran recently reported that all the cholesterol in spinal fluid was esterified in normal persons, but their normal group included patients with convulsive disorders in whom Selbache and Trappe reported both forms of cholesterol present.[24]

The average total spinal fluid cholesterol value found by Poser and Curran is about the same as the free cholesterol concentration found by us, namely 0.1 mg. per 100 cc. All spinal fluid specimens studied in our laboratory have contained measurable quantities of free cholesterol, while Poser and Curran had normal specimens which did not contain any cholesterol. Biochemically, the cholesterol procedure proposed by us is not hydrolyzing esterified cholesterol to form free cholesterol.[5] Possibly, the differences between the procedures utilized by Poser and Curran and those used in our laboratory may explain the discrepancies. First, we have found that spinal fluid which is centrifuged and then frozen contains an insoluble mass upon thawing; this mixture is difficult to pipet properly for lipid extraction, and, consequently, we do not freeze the specimens studied in our laboratory. This insoluble mass may contain lipids, and hence the significant difference in the methods. Second, the low total cholesterol value, in comparison to our data, may be the result of errors inherent in extracting lipids on a macroscale from a dilute lipid solution. Third, assuming that the average normal total cholesterol of spinal fluid by their procedure is 0.11 mg. per cent, that the losses of esterified and free cholesterol are the same in their procedure, and that the free cholesterol concentration is 28% of the total cholesterol, then 0.0308 mg. per cent should be free cholesterol (0.11×0.28). Since the least amount of cholesterol determinable by their method was 0.03 mg. per cent, we would expect that, by their method, free cholesterol could not possibly be detected in normal spinal fluid.

Lier reported total lipid values in normal spinal fluid similar to those reported here (0.5 to 1 mg. per cent),[25] although the majority of authors do not agree with the value found in this study.[1]

The data presented here indicate the possibility that neutral fat exists in the spinal fluid. Future experimentation will have to establish this.

Table 3 shows the comparison of lipids in normal spinal fluid with fasting normal serum and the gray and white matter of the brain. It should be first pointed out how dilute the lipids are in the spinal fluid. All the data are expressed in milligrams per 100 cc. or 100 gm. of fresh weight. For example, in the spinal fluid there is 0.4 mg. of total cholesterol per

TABLE 3
THE COMPARISON OF LIPIDS IN NORMAL SPINAL FLUID WITH FASTING NORMAL SERUM, GRAY AND WHITE MATTER

Lipid	Spinal fluid[1]		Fasting serum[2]		Gray matter[3]		White matter[3]	
	Mg. per cent	Per cent of total	Mg. per cent	Per cent of total	Mg. per 100 gm. of F.W.[4]	Per cent of total	Mg. per 100 gm. of F.W.	Per cent of total
	1	2	3	4	5	6	7	8
Cephalins	0.091	7	18	2	700	12	2100	12
Lecithin	0.168	13	119	13	1100	18	1100	8
Sphingomyelin	0.087	7	42	5	600	10	3000	17
Total phospholipid	0.370	30	184	21	3900	65	7800	43
Cerebroside	0.059	5	27	3	1100	18	5800	32
Total cholesterol	0.415	33	180	20	1000	17	4500	25
Cholesterol ester	0.292	23	126	14	0	0	0	0
Free cholesterol	0.109	9	54	6	1000	17	4500	25
Neutral fat	0.403	32	484	55	0	0	0	0
Total lipid	1.254	—	876	—	6000 (cal.)	—	18,100 (cal.)	—

1. Present data
2. Tourtellotte, W. W., et al. Unpublished data[5]
3. LeBaron and Folch[21]
4. Fresh weight

100 cc., in the blood about 430 times more, in the gray matter about 2,400 times more, and in the white matter, about 11,000 times more. These differences are much less if the data are expressed in terms of milligrams of total protein. In spinal fluid, there are 13.8 μg. of total cholesterol per mg. of protein (415 μg. per 30 mg.) and in blood, 24.3 μg.

$$\frac{(180{,}000\ \mu\text{g.})}{7{,}404\ \text{mg.}}$$

—only about 2 times instead of 400.

Apparently the lipid profile of spinal fluid more closely resembles that of serum than either white or gray matter. The spinal fluid contains cholesterol ester and neutral fat as does the serum, but the normal brain tissue does not. The spinal fluid also resembles the serum in the percentage distribution of the various lipids.

In columns 2 and 4 under per cent of total, note the agreement between cephalins, 7 and 2 (spinal fluid and serum, respectively); lecithin, 13 and 13; sphingomyelin, 7 and 5; total phospholipid, 30 and 21; cerebroside, 5 and 3; total cholesterol, 33 and 20; cholesterol ester, 23 and 14; free cholesterol, 9 and 6; and neutral fat, 32 and 55. On the average, the serum concentration for these various lipids is 514 times that of the spinal fluid, with a range of 193, and then 432 to 1,200, and then 710. If the data are expressed in terms of microgram of lipid per milligram of protein, the difference between the various lipids in spinal fluid and serum is only a factor of 2 with a range of 0.8 and then 1.7 to 4.7, and then 2.8. These similarities (content and per cent distribution) may indicate that one of the mechanisms of formation of normal spinal fluid lipid may be from the serum across the blood–spinal fluid barrier. A number of experiments could be designed to test this hypothesis.

At the present time, we are studying spinal fluid and fasting blood from patients with multiple sclerosis.

SUMMARY

1] An analytic scheme is presented for the duplicate determination of cephalins, cephalins plus lecithin, sphingomyelin, total phospholipid, total sphingolipid, total cholesterol, free cholesterol, and total lipid in 10 cc. of cerebrospinal fluid. From these determinations, the lecithin, cerebroside, cholesterol ester, total phospholipid, and neutral fat concentration can be calculated. The tests of the method were briefly reviewed.

2] The average, the s.e.m., and the range were given for these lipids in 27 healthy men

and women 20 to 34 years old. Sphingomyelin, total phospholipid, and total lipid were significantly higher in men than in women; free cholesterol was lower in men. The rest of the lipid fractions were similar in both groups.

3] These data confirm certain reports in the literature that lumbar cerebrospinal fluid from normal individuals contains such lipids as cholesterol and phospholipids. In addition, our data indicate for the first time that cephalins, lecithin, sphingomyelin, cerebroside, and neutral fat are also present in normal spinal fluid.

4] The lipids in the normal spinal fluid were compared to those in normal fasting serum. On the average, the lipids in the serum were 514 times more concentrated. Furthermore, a similarity was apparent in the per cent distribution of the lipids in normal spinal fluid and serum. However, if the data were expressed in terms of micrograms of lipids per milligram of protein, the differences between the various lipids in serum and spinal fluid were approximately 2.

ACKNOWLEDGMENT

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A rare form of ectodermal dysplasia

Mental retardation, congenital skin disorder, and congenital spastic disorder

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THE MORE COMMONLY KNOWN ectodermal dysplasias[1] are tuberosclerosis, von Recklinghausen's disease (neurofibromatosis), and xeroderma. Anomalies of mesodermal origin, such as the Sturge-Weber syndrome and Lindau's disease, are justifiably termed ectodermal dysplasias.[2]

The concept of a relationship between mental defect and cutaneous changes was expressed by Brissaud.[3] The term congenital ectodermal defect was first used by J. Christ in 1913, cited by W. H. Goeckerman.[4] Cockayne[5] described approximately 200 primary cutaneous congenital anomalies. Yakovlev[6] referred to these as neoplastic malformations that "occupy an intermediary position between simple maldevelopment of tissues with their secondary hyperplasia (congenital dystrophia) and true tumor (blastomata), often partaking of both," and used the term congenital ectodermosis.

On the basis of the often observed hereditary factor, Adrian in 1901, Prieser and Davenport in 1918, and Kaufman[7] concluded that these conditions represented deep-rooted anomalies of the *anlage*, where ectodermal and mesodermal elements may alternately prevail. Yakovlev feels that one should think in terms of an ectodermal-mesodermal complex.

Following an extensive clinical and genetic study and a thorough review of the literature, the Swedish workers, Sjörgren and Larsson,[8] described a yet unnamed syndrome consisting of oligophrenia, congenital ichthyosis, spastic disorders, and, less consistently, degenerative retinitis. These workers believe that, in many patients, a genetic etiology exists for syndromes consisting of 2 or more of these conditions and that the combinations of oligophrenia and congenital ichthyosis (no spastic disorder) and oligophrenia and spastic pyramidal disorder (no ichthyosis) are rather rare conditions. They present evidence that their syndrome is genetically determined through a monohybrid, autosomal, recessive type of transmission of the heritable trait.

Yakovlev[9] says that, "theoretically one might expect a similar incidence (1:1,000) of this syndrome among feeble-minded persons of other countries," and concludes that this new syndrome is of distinct interest and should be known, especially to workers in the field of mental deficiency. Larsson recommends that material concerning syndromes of the type in question be reported in sufficient detail to be of value to other research workers for pooling case material and for comparisons, differential diagnosis, coincidence analysis, and genetic analysis.

A patient with an I.Q. of 46, congenital spastic disorder, congenital skin disorder (ichthyosis), hyperpigmentation, hypertrichosis, and epilepsy is described. Benda and Yakovlev thought the patient's skin condition resembled the ichthyosis seen by them in other adult patients with ectodermal dysplasia. However, the dermatologist, John R. Strauss, believed this was not ichthyosis. MacGillivray states that dermatologists generally agree that ichthyosis and xeroderma are merely different degrees of a single disease. Dr. Sjörgren writes in a personal communication on December 4, 1957, that Prof. Sven Hallerstrom says our case is not ichthyosis.

The writer personally examined 13 rela-

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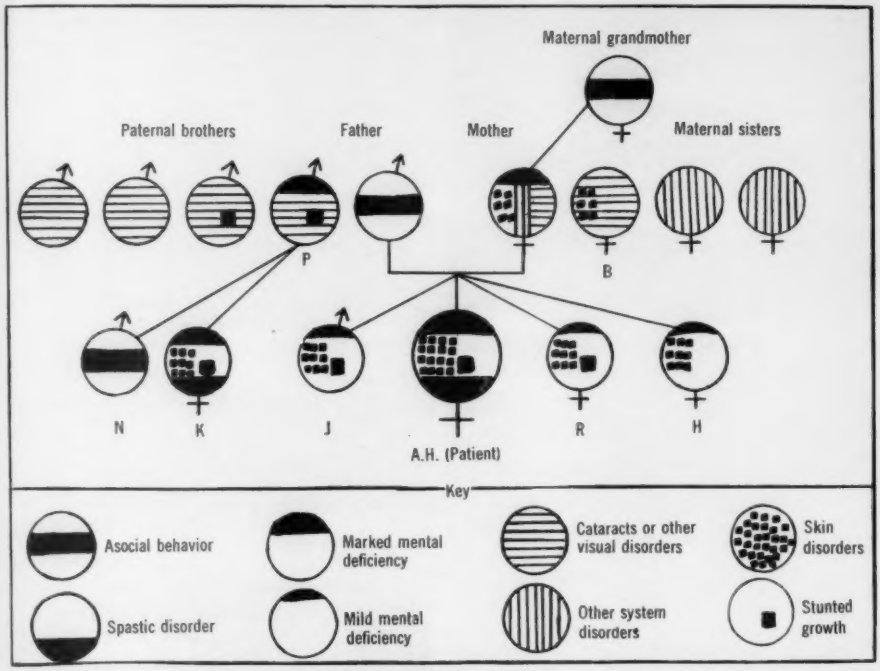

Fig. 1. Pedigree chart

tives—3 siblings, 4 paternal first cousins, 1 maternal first cousin, 2 maternal second cousins, 1 paternal uncle, and 2 maternal aunts—and took the family histories of 33 other relatives in 4 generations. The family were originally Austrian peasants; the paternal side was from the Ukraine and the maternal side from Hungary.

Consanguinity was admitted by 2 relatives on hearsay; one said the patient's paternal first cousin was the patient's paternal grandfather; and the other that the patient's father's brother or uncle married within the family.

Case 1. A 45-year-old white woman was admitted to the Walter E. Fernald State School on July 26, 1957. She was mentally deficient and unable to take care of herself.

At birth after a full-term pregnancy the patient was "covered with hair just like an ape, and her back was deformed." She had many scattered pigmented nevi and an extensive pigmented area on her back. The patient was the first of 4 pregnancies and was delivered by instruments after two or three days' difficult labor. Her mother was 19 and her father 30.

At 11 months of age, she had "periods of stiffening and becoming black in the face." These episodes lasted ten or fifteen minutes and were followed by confusion. The patient crawled at 8 months, had her first tooth at 9 months, and walked and talked at 1 year. Mental retardation was first noted when she was 4 or 5. From 5 to 7, nevi and hair grew more profuse, and her walk became more abnormal. At 6, lameness developed gradually and the patient was admitted to a children's hospital. A diagnosis of "spastic diplegia" was made.

At 7 she started the first grade of St. James School in Salem, Mass., "but she only lasted two weeks" because "she was silly and would laugh, giggle and play the harmonica in class." In May 1919, a diagnosis of congenital skin tumors and subnormal mentality was made at Boston hospital.

At 9, the patient was admitted to a Boston psychopathic hospital and there her behavior was described as "excitable, yet slow in action, tidy in habits, inclined to be destructive, laughing easily without apparent reason, and willful and unkind to little children." At 10, she was admitted to a state school from which she was discharged four years later with the following diagnosis: [1] mild grade moron (MA 5– plus and I.Q. 61) and [2] endocrine disturbance.

Fig. 2. Physiognomy. Note hypertrichosis on areas other than nevi.

Until admitted to the Walter E. Fernald State School, the patient lived with her parents. Her mother died in 1940, and she then lived with her father until he died in February 1957. A married sister lived downstairs and supervised her. In these circumstances, apparently, the patient was able to care for herself after a fashion.

Until the patient was 28, she had infrequent convulsive episodes characterized by sudden loss of consciousness, followed by generalized tonic and then clonic contractions and postictal confusion. These episodes lasted as long as fifteen minutes. Loss of sphincter control or tongue biting did not occur. Anticonvulsive medication was never administered.

Menarche was at 13, and the cycle was subsequently normal. She was sexually abused as a child and had gonorrhea at 7.

Both paternal and maternal family trees are filled with asocial behavior and visual disorders. On the paternal side, in addition, stunted growth occurs, and on the maternal side, mental deficiency, skin disorders, and reduced life span are found. Mental deficiency, spastic disorders, skin disorders, other system disorders, and stunted growth are present in the patient's siblings (Fig. 1).

Relatives with asocial behavior included those with violent dispositions, individuals who were "very filthy," and those who disregarded law and authority, were sexually promiscuous, sexually perverted, or alcoholic.

Visual disorders were either described as "bad eyes" or "cataracts." The patient's mother and paternal uncle P had bilateral cataracts; her father and his other 2 brothers had "bad eyes;" her maternal aunt B and 3 of B's daughters were myopic.

Average height was 4 ft. 6 in. for stunted females and 5 ft. 2 in. for stunted males. Mentally deficient relatives had I.Q.'s ranging from 46 to 74. The patient's father, mother, 2 paternal uncles, 2 sisters, and 1 brother were tested in June 1921, and all except her father were found to be mentally deficient.

Skin disorders among relatives consisted of nonvascular nevi of the following types:[10] pigmentosis and pilosis (mother), pigmentosis only (maternal aunt and all 3 siblings), pigmentosis and verruca (paternal cousin K), and dry skin (siblings H and R).

Relatives also had cardiovascular, respiratory, and genitourinary disorders. Sibling H has had operations for thyroid, pharyngeal, and uterine tumors.

Relatives extremely mentally deficient died in their late 40's, while those with higher I.Q.'s died or are still living in their 60's and 70's.

The patient was pleasant and cooperative and smiled readily, but inappropriately, at times. The patient was unable to give dates or names of

Fig. 3. Note posture, lordosis, obesity, and nevi.

Fig. 4. Extensive pigmented, lichenified lesion in back extends to midbuttock region bilaterally. Note sharp well defined borders of this and the smaller lesions.

places or persons but was generally oriented to her surroundings; affect was blunted and cerebration was extremely retarded. She knew the value of money but could not comprehend the 100-7 test.

Results of psychologic testing were: Revised Stanford-Binet Form L, mental age 6 to 10 years; I.Q. 46; Healy Picture Completion Test II, 8 illogical choices out of a possible 10. This lack of judgment was also reflected in the patient's inability to detect absurd elements in simple statements. She showed no incentive toward attention, effort, or compliance with instructions. However, she was not indifferent to repeating series of digits, a task which she carried out more competently than is common at this mental level.

The patient's blood pressure varied from 136/84 to 190/120. Her genitals were normal. Tone was increased in the patient's legs. Strength was normal. No atrophy or fasciculation was found. Abdominal reflexes were active and equal; jaw jerk was overactive; tendon reflexes were active and equal in her arms but overactive in her legs and greater in the right leg than in the left. She had unsustained ankle clonus which was slightly more active in the right ankle; Babinski and Chaddock's reflexes were positive on the right, and Hoffman reflexes were positive bilaterally. Her gait was lurching, spastic, and scissor-like. Coordination was intact. A bizarre pattern of hypalgesia involved the face, extremities, and upper trunk but did not fit any anatomic distribution. Vibratory and position sense, graphesia, and 2-point discrimination were normal.

Visual acuity was 20/20 in each eye. Visual fields were full by confrontation; fundi were normal; disks were questionably pale. She had no papilledema or abnormal pigmentation. Her pupils were round, regular, and equal and reacted well to light and convergence.

The patient's third, fourth, and sixth cranial nerves were intact as were the other cranial nerves. She had no facial weakness or asymmetry. Her speech was slightly labored, explosive, and loud, but she had no aphasia.

Figures 2, 3, 4, and 5 show the patient's physiognomy; obesity; marked lordosis; widely scattered, dark brown nevi; extensive hyperpigmented, thick, rough lesion; and facial hypertrichosis.

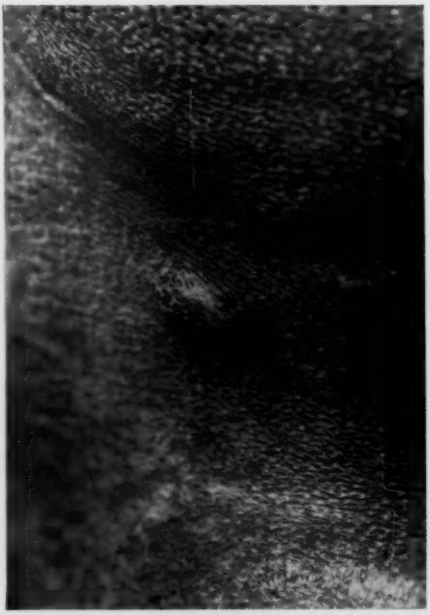

Fig. 5. Close-up of Figure 4. Note ichthyotic appearance of skin. Compare with figures 5 and 6 in Sjörgren-Larsson monograph. Note soft, movable, nonadherent nodules, not unlike a lipoma. Note hair in lower right corner.

LABORATORY DATA

Urinalysis: Normal, negative sugar and albumin; 17-ketosteroids, 5 mg. per twenty-four hours; corticosteroids, 3.7 mg. per twenty-four hours (normal, 2 to 7 mg. per twenty-four hours); Reddy, 3.3. mg. per twenty-four hours; Nelson, 3.79 mg. per twenty-four hours; phenylpyruvic acid, negative; creatine, 110 mg. per cent.

Hematology: Red blood count, 4.58; white blood count, 7,900; segmented neutrophils, 61%; lymphocytes, 39%; hemoglobin, 96%, 14 gm.; sedimentation rate, 2 mm. per hour; hematocrit, 48; mean corpuscular volume, 140μ; mean corpuscular hemoglobin, 45%; reticular count, 34,000.

Chemistry: Nonprotein nitrogen, 45 mg.; fasting blood sugar, 130 mg.; total cholesterol, 289 mg. per cent; protein-bound iodine, 6.8 μg. per cent; total iodine, 6.8 μg. per cent.

Serology: Hinton test, negative.

Roentgenograms: Chest, negative; long bones, negative; spine, moderate hypertrophic changes on the anterior margin of several lumbar and middorsal vertebrae; skull, calcification of the petroclinoid ligaments, plaque in posterior parietal area which appeared to be related to the falx.

Cerebral spinal fluid: Lumbar puncture not done because of back lesion; administrative difficulties precluded cisternal puncture and pneumoencephalogram.

Electroencephalogram: Diffusely abnormal because of asymmetries in the right anterior hemisphere and spike-like activity in the right midtemporal, right frontal, and occipital areas.

These findings were those of specialists in ophthalmology, dermatology, radiology, and electroencephalography.

Case 2. K. H. (Paternal first cousin K, see Figure 1), a 40-year-old white woman, was examined by the author and found living alone in shocking filth and squalor.

She had been discharged from a state institution for the mentally deficient several years ago, apparently because of insistence of relatives. The patient was classified as a high-grade imbecile and was friendly and cooperative in a docile way. She obviously had no insight or concern about her circumstances.

She was 4 ft. 7 in. tall and had moderate kyphosis. She had widely scattered, verrucous nevi, especially on her face. A few of the nevi were light brown; the rest were not pigmented. Amount and distribution of hair was normal. Her gait was moderately spastic. Reflexes were active in her arms and hyperactive in her legs. She had positive left Babinski reflex. Her cranial nerves were intact, and her speech was relevant, coherent, and without dysarthria or aphasia.

DISCUSSION

In reviewing the literature, one is impressed by several facts:

1] No generally accepted diagnostic term exists, although the terms ectodermal and dysplasia are frequently used, modified by such terms as congenital and hereditary.

2] Many combinations of signs and symptoms have been described and labeled as specific syndromes and diseases (see table).

3] In many instances, ample evidence is found of genetic etiology.

4] The combination of low-grade mental deficiency, skin disorder, and spastic disorder other than in the monograph by Sjörgren and Larsson has not been described.

5] The term ichthyosis has many connotations which are not altogether agreed on even by dermatologists. Interested individuals are invited to compare Figures 3 and 4 with Figures 5 and 6 in Sjörgren and Larsson's monograph. Obviously some of these congenital neurocutaneous syndromes overlap each other clinically and pathologically.

Apparently, hairy, pigmented moles are nonspecific and no different from birthmarks encountered in otherwise healthy people, except that the moles are more numerous and often are larger.[6,10] Hypertrichosis is due to a variety of causes, but excessive hypertrichosis present at birth or appearing early in childhood and localized excessive growth of hair in nevi usually are hereditary. According to Danforth,[11] the most common type of hypertrichosis in women is on the upper lip and is a definite hereditary dominant trait. This trait shows a correlation of 0.8 between mothers and daughters. Hypotrichosis is apparently more common.[1,4,12–14] Anhidrotic ectodermal dysplasia is frequent and is said to be either dominant, recessive, or sex-linked.[4,14–18] Epilepsy often complicates a variety of ectodermal dysplasias.

Apparent endocrine disturbances, suggesting involvement of pituitary, thyroid, parathyroid, and testicular glands, have been observed in various ectodermal dysplasias. Rud, cited from Sjörgren and Larsson, considered patients of this type to have pluriglandular disturbances. Thannhauser[7] discusses endocrine symptoms in neurofibromatosis and osteitis fibrosa cystica disseminata; Weech,[13] in hereditary ectodermal dysplasias. However, biochemical evidence to support these so-called endocrine disturbances is absent. Neuropathologic lesions have been found in the pituitary, pin-

Manifestation	*von Recklinghausen's disease*	*Tuberous sclerosis*	*Xeroderma*	*Rud's syndrome*	*Berier's disease*	*Kaposi's disease*	*Xerodermic idiocy, De Sanctis and Cacchione*	*Anhidrotic ectodermal dysplasia*	*Hidrotic ectodermal dysplasia*	*Rothmund's syndrome*	*Werner's syndrome*	*Progeria, Hutchinson-Gilford disease*	*Laurence-Moon-Biedl syndrome*	*Klippel-Trenaunay's syndrome*	*Sjörgren-Larsson syndrome*	*A. H.*
Mental deficiency	±	+						±								+
Ichthyosis, roughened skin		+		+							+				±	+
Spastic disorder		±													+	+
Retinal degeneration													+			+
Hyperpigmentation		+	+	+	+	+	+		+	+					±	+
Hypertrichosis								+			+	+				+
Hypotrichosis		+														+
Nevi	+	+														+
Cataract, other eye disease	+	+														+
Epilepsy	±	±	±	+					+	+				+		+
Anhidrosis								+								+
Hidrosis						+			+							+
Cutaneous atrophy											+	+				+
Hyperkeratosis of palms and soles																+
Dystrophy of nails									+							+
General infantilism				+					+					+		+
Stunted growth					+		+			±						+
Reduced life span																+
Telangiectases						+			+		+	+				+
Other systemic abnormalities																+
1. Cardiovascular	±	±						?	?	+	+	+	+	+		+
2. Musculoskeletal	±	±			+											+
3. Genitourinary	±	±					+			+						+
4. Respiratory	±	±														+
5. Gastrointestinal	±	±														+
6. Endocrine	±	±														+

± sign or symptom may or may not be present.

Note the relative rarity of the combination of mental deficiency, ichthyosis, and spastic disorder, and that hypertrichosis is present only once.

eal, adrenal, and other endocrine glands in neurofibromatosis.[2] Endocrine studies were remarkably normal in our patient.

From the standpoint of genetic analysis, the material is not as complete as could be desired, and the information regarding consanguinity is not definitive. The author believes that these difficulties will be encountered frequently in this country because of the immigrant population. However, the data presented show that 2 women had the triad of low-grade mental deficiency, skin disorder, and spastic disorder. A recessive, partially sex-linked[19] type of inheritance for the triad is strongly suggested. (The mode of inheritance was monohybrid autosomal recessive in Sjörgren and Larsson's 24 patients. However, in 2 families—3 and 1A—only women were affected.)

A sex-influenced[19] type of inheritance in which certain autosomal genes manifest themselves in only one sex, or with a preference for one sex, is an equal possibility and might be considered more consistent with the monohybrid autosomal recessive type in the Sjörgren-Larsson cases.

CONCLUSIONS

1] A rare combination of oligophrenia, congenital spastic disorder, and congenital skin disorder is reported in 2 women.

2] If interested workers are aware of this syndrome, expected incidence (1:1,000) among feeble-minded persons of the United States and other countries might be found.

3] The ethnic heterogeneity of this country makes the study of medical genetics very difficult.

4] The term ichthyosis will probably cause further confusion.

A report and photographs of Case 1 were sent to Dr. Torsten Sjörgren, Stockholm, Sweden. He replied that he did not consider that this case belonged to the syndrome described by him and Dr. Larsson, but that it represented a separate syndrome.

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Cerebrovascular Disease:

II. The smaller intracerebral arteries

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THE DEGREE OF ATHEROSCLEROSIS of the large vessels along the base of the brain often does not correlate with the severity of tissue changes within the brain. Extensive atherosclerosis frequently occurs when clinical or pathologic evidence of brain involvement is absent. Further search should be made for a better correlation between cerebrovascular disease and tissue alterations.

The most logical procedure is to study some of the smaller intracerebral arteries. The smaller intracerebral arteries can be divided into 2 groups: those varying in size from 150 to 500 μ. in diameter and those of the arteriolar size below 150 μ. in diameter. The present study is limited to the larger of these vessel groups.

In 1884, Obersteiner[1] published one of the first studies on these intracerebral arteries. He described the internal elastic lamina as a very delicate membrane which disappeared as the caliber of the vessel diminished. The muscle media was composed of spindle-shaped muscle fibers which encircled the inner layers of the blood vessel. He described the adventitia as a delicate layer of connective tissue which was not attached to the muscle layer; a free space existed between these 2 coats. He described calcareous deposits which could occasionally be observed in the adventitia. When extensive, these deposits would spread to the muscular coat. Such calcareous deposits were even observed in patients under 10. Fatty deposits were also observed in the muscular coat and appeared as small, point-like fat granules filling the muscular layer. These fatty changes occurred in healthy as well as diseased brains and in young subjects as well as old.

Binswanger and Schaxel[2] studied these smaller arteries in brains from newborn subjects to subjects 60 years old. They believed smaller artery structure was similar to that of the larger vessels, except that the media has less elastic fibrils. With increasing age, the layers of these arteries increase irregularly in thickness. The elastic tissue did not increase as much as the media. In individuals over 50 years old, the elastic and muscle tissue of the media decreases; the connective tissue in the septa and in the adventitia increases.

Häckel[3] studied 13 patients 15 days to 50 years old. He believed that the cerebral arteries differed from systemic arteries elsewhere because they had a thick internal elastic lamina, no external elastic layer, and a poorly developed adventitia. He believed that the splitting of the internal elastic lamina was an age change.

Benninghoff[4] described the internal elastic lamina as a fenestrated membrane. He believed that this membrane divides early to give rise to a lamellated appearance. In middle life, the elastica no longer multiplies but is slowly replaced by an increasing connective tissue which appears whenever there is a space resulting from degeneration.

Ranke[5] did not believe that the elastica was a distinct layer but that, with the connective tissue, the elastica forms a widespread mesenchymal net which is continuous from the subendothelium to the adventitia. In a fully developed artery, the inner and outer connective tissue layers are connected by radial bridges forming spaces in the internal elastic lamina.

CASE MATERIAL

The present study was carried out on the brains of 100 consecutive subjects. Studies

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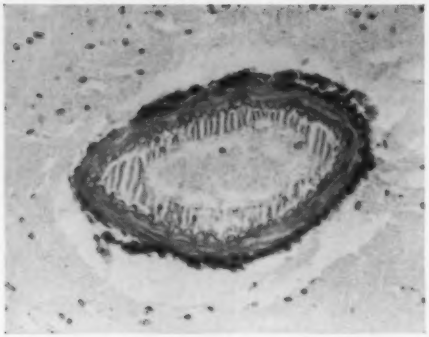

Fig. 1. Normal small artery of 175 μ. from a patient aged 39 years ($\times$ 200)

Fig. 2. Thick adventitial layer completely surrounding the media (Van Gieson's stain $\times$ 140)

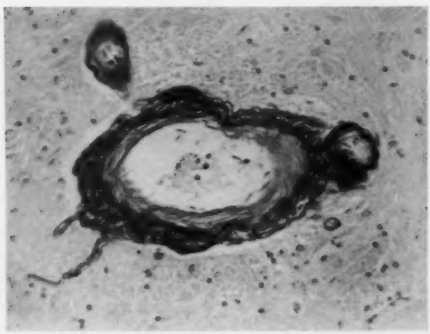

Fig. 3. Compression and replacement of the outer medial layer by adventitial proliferation. Note the layer of muscle tissue that still surrounds the lumen. (Van Gieson's stain $\times$ 220)

were also available on the changes within the large arteries along the base of the brain in these same subjects. Blocks were taken from the frontal, temporal, and occipital areas, the basal nuclei, the hypothalamus, and the brain stem. All sections were stained with hematoxylin-eosin stain, Van Gieson's stain, and Weigert's elastic tissue stain.

Normal arteries of 150 to 500 μ. diameter. These arteries have a distinctive structure which is fairly characteristic of muscular arteries. The intima consists of a well-formed, wavy internal elastic lamina and an endothelial layer. The endothelium is often difficult to discern and consists of a delicate membrane composed of a single layer of flattened cells whose nuclei are elongated or oval shaped and arranged with their long axes in the direction of the blood flow.

The internal elastic layer is directly under the endothelium and is a well-developed, wavy, homogeneous membrane. Normally this membrane is not lamellated and appears to be a fairly solid membrane with no variations in thickness or staining properties (Fig. 1).

The media is composed of muscle fibers arranged in a circular fashion. The thickness of the media is variable, consisting of 5 to 20 intertwining layers of muscle fibers. The muscle fibers are separated by fine strands of connective tissue which often cannot be detected except by careful study under high magnification. Elastic fibrils are generally not found in the muscular media. Normally, a sharp demarcation occurs between the media and the internal elastic lamina.

The adventitia is the most poorly developed of all membranes and, in many arteries, may be entirely absent. Usually, the adventitia is composed of a few fibrous strands placed irregularly about the vessel (Fig. 1). Some vessels show a very fine connective tissue layer completely surrounding the vessel. A sharp separation is found between the media and adventitia, but these layers are closely approximated and no distinct separation occurs between them. The adventitial connective tissue normally has no tendency to infiltrate into the outer medial wall.

Pathologic arterial changes. The vessels throughout the cerebral hemispheres show similar changes and will be described as a unit.

The elastica undergoes very little alteration and, for the most part, remains wavy and intact. In isolated cases, portions of the internal elastic membrane become split, leaving 2 or 3 layers, the outer of which may be fragmented. No other internal changes are observed. The intimal connective tissue increase seen so commonly in the larger arteries apparently does not occur in these smaller vessels.

In these arteries, the earliest and most consistent changes occur within the adventitia. An early, mild increase occurs in the thickness of the adventitia only around certain areas of the vessel or around the entire vessel. The adventitial connective tissue may continue to increase in thickness until a heavy layer is formed which may be as prominent as the media (Fig. 2). Even at this stage, a fairly sharp demarcation may exist between the media and adventitia.

In most cases, the proliferation is most prominent in the inner layer of the adventitia. This causes a gradual compression of the muscular media, and, ultimately, most of the media is compressed and replaced by heavy collagenous fibers. Often, only a thin layer of muscle tissue remains which surrounds the vessel lumen (Fig. 3). Ultimately, the entire medial layer is replaced so that the entire vessel wall is composed of collagenous tissue which may become acellular and even hyalinized.

Generally, this adventitial increase does not cause thickening in the vessel wall. The proliferative process usually does not encroach upon the vessel lumen—which in most cases remains patent and of normal size. Occasionally, the proliferative process is most prominent in the outer adventitial layers. In such cases, the proliferation may extend outward into the surrounding tissues in an irregular fashion (Fig. 4). When this type of adventitia proliferation occurs, the vessel wall invariably becomes thickened. Continued connective tissue proliferation can, in time, produce a narrowing, or even complete occlusion, of the vessel lumen.

Another type of adventitial change is often encountered. The inner adventitial layer begins to proliferate and slowly infiltrates the outer medial layers. This medial infiltration is diffuse, implicating the entire media but not causing a striking increase in the thickness of the adventitia. The infiltrating collagen continues to increase in thickness until all the muscle fibers are replaced, leaving a relatively thin vessel wall composed entirely of collagen (Fig. 5). When this type of diffuse collagenous infiltration occurs, the vessel lumen is never involved and the vessel wall always retains its original thickness.

Changes within the media are almost always due to a primary proliferative process within the adventitia. Primary changes within the media are generally not encountered. Apparently, the chief degenerative changes within

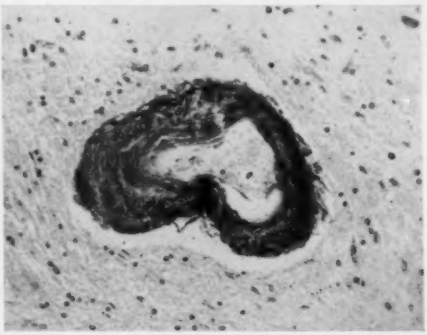

Fig. 4. Proliferation of the outer adventitial layers resulting in an extension of the collagen into the surrounding tissues and resulting in a marked increase in the vessel wall (Van Gieson's stain × 220)

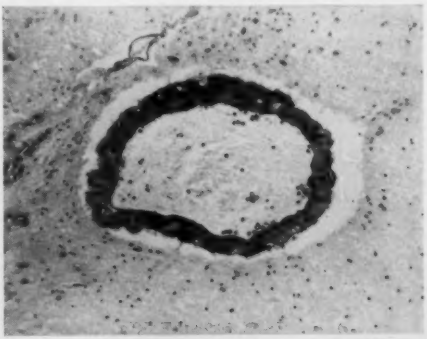

Fig. 5. Completely fibrotic vessel of normal thickness. No demarcation of layers can be seen. (Van Gieson's stain × 140)

TABLE 1

Age	Degree of involvement: Normal or minimal	Moderate	Marked or severe
0 to 10 years	9 or 100%		
11 to 20 years	8 or 100%		
21 to 30 years	6 or 85%	1 or 15%	
31 to 40 years	3 or 60%	1 or 20%	1 or 20%
41 to 50 years	7 or 64%	1 or 9%	3 or 27%
51 to 60 years	7 or 30%	5 or 22%	11 or 48%
61 to 70 years	5 or 50%	3 or 30%	2 or 20%
Over 70 years	8 or 30%	7 or 26%	12 or 44%

these smaller arteries are the result of adventitial changes.

In those vessels which have been completely replaced by collagenous overgrowth, the heavy layers of collagen may become partially or completely hyalinized. Occasionally, the outer layers of these vessels become filled with irregular calcium deposits which may replace the entire vessel wall.

One very striking feature about the changes in these vessels is the associated changes in the surrounding tissues. Invariably, when arteries of this caliber become narrowed or occluded, the surrounding parenchyma degenerates. The extent of the parenchymal changes will naturally depend upon the severity and the number of arteries involved.

The degree of artery involvement varies greatly, even in the same brain; some arteries are completely fibrotic, while others show minimal changes. Generally, the changes within the arteries of the cerebral cortex and white matter are fairly uniform. The greatest variation occurs in the arteries of the basal nuclei, hypothalamus, and brain stem. The arteries of the brain stem invariably show a lesser degree of involvement than those of the hemispheres, while the vessels in the basal nuclei and hypothalamus show much more severe changes. Not uncommonly, the arteries in these latter areas will be completely fibrotic, while the vessels of the hemispheres reveal no changes or only a beginning proliferation within the adventitia.

DISCUSSION

Apparently, the smaller intracerebral arteries of 150 to 500 μ. in diameter have a uniform type of degenerative alteration which is strikingly different than the changes within the larger arteries along the base of the brain. Practically the only change observed in these smaller arteries is an adventitial connective tissue proliferation which ultimately results in a complete vascular fibrosis. Intimal changes or fatty deposition almost never results. Because of this strikingly characteristic change, an attempt was made to detect in our studies factors that might play an etiologic role in the production of these vascular changes.

TABLE 2

CHANGES IN SMALL CEREBRAL ARTERIES AS COMPARED TO ATHEROSCLEROSIS OF LARGER ARTERIES ALONG BASE OF BRAIN

Degree of change in smaller arteries	Degree of atherosclerosis of large arteries: None	Mild (1 to 5 plaques)	Moderate (5 to 9 plaques)	Severe (over 10)
No changes	22 or 41%	20 or 38%	7 or 13%	4 or 8%
Moderate changes	3 or 16%	7 or 39%	1 or 6%	7 or 39%
Severe changes	10 or 34%	6 or 21%	6 or 21%	7 or 24%

TABLE 3
RELATION OF DEGENERATIVE CHANGES OF SMALL ARTERIES TO SOMATIC DISEASE

	Normal arteries	*Severe changes*
Men	21	16
Women	16	12
Blood pressure over 170/100	4 or 12%	6 or 22%
Heart weight over 450	10 or 36%	12 or 50%
Cardiac disease	8 or 22%	7 or 25%
Kidney disease	4 or 10%	2 or 8%
Malignancy	9 or 24%	10 or 36%
Other disease	16 or 44%	9 or 31%

Age correlation. Table 1 lists the degree and frequency of the vascular changes compared to the patient's age. As in most degenerative conditions of the vascular system, some correlation occurs with the age of the patient. Fibrosis of these smaller intracerebral arteries does not appear until the third decade of life and is not severe until the fifth decade. However, a consistent correlation with age stops at this point. As can be seen from Table 1, in the seventh decade of life 50% of patients had little or no change within these small arteries and only 20% had severe fibrosis. Even past 70 years, 30% of the patients had little vessel change.

These observations certainly suggest that factors other than age must play an important role in the production of these degenerative vascular changes. Undoubtedly, these changes occur more frequently in older age groups, but age alone is not the final answer to such changes.

Correlation to changes in larger basal arteries. In a previous report,[6] a detailed study was made of the atherosclerotic changes in the larger arteries along the base of the brain in 173 unselected subjects. The present study was also taken from these same cases so that a comparison could be made between the severity and frequency of the degenerative vascular changes in the larger vessels and those observed in the present study. Table 2 outlines such a comparative study.

For this report, patients within the first decade of life were omitted; vascular alterations were not observed in these patients. A study of Table 2 will immediately reveal that little correlation is found between the changes observed in these vessels of various size. Of the subjects with no fibrosis of the smaller arteries, 21% had severe changes within the larger basilar vessels. Even more striking was the fact that 55% of the subjects with severe or complete fibrosis of the smaller intracerebral arteries had little or no change in the larger arteries along the base of the brain.

When one considers the different nature of the pathologic alterations in these different sized vessels, one is not surprised at this lack of correlation as to frequency and severity of change. Certainly, the striking difference in the histologic alterations in these vessels would indicate that the etiologic factors involved probably are quite different. Under such circumstances, any correlation in the frequency of the degenerative changes in these vessels would be surprising.

Correlation with somatic disease. In most of the 100 cases comprising this study, complete clinical and autopsy studies were available. Although the present series is much too small for an accurate correlation of the vascular changes with somatic factors, such a study still might offer certain significant leads which might be helpful in later, more extensive studies.

Table 3 is a comparative study of somatic changes in subjects with no changes in the intracerebral arteries, compared to those subjects with severe degenerative changes. None of the disease categories appeared to play a significant role in such vessel changes. Even

severe cardiac diseases showed little difference in the degree of intracerebral vascular change. The only significant change was observed in cases of definite hypertension or cardiac enlargement. In these subjects, although small in number, severe vascular fibrosis was almost twice as frequent as in subjects with normal vessels. Apparently, hypertension does play a definite role in the production of degenerative changes within these smaller intracerebral arteries.

CONCLUSIONS

1] A study was made in 100 consecutive cases of intracerebral arteries measuring 150 to 500 μ.

2] The chief degenerative change is limited to the adventitia which undergoes proliferation and ultimately replaces the entire vessel wall, causing a fibrotic vessel. Intimal changes or fatty deposits almost never occur.

3] Vascular fibrosis first appears in the third decade of life but is not severe until the fifth decade. Even in elderly subjects, over 50% of the patients will show little or no change within these smaller arteries.

4] No correlation is found between the changes in these arteries and atherosclerosis in the larger arteries along the base of the brain. In 50% of cases showing severe fibrosis of the smaller arteries, little or no atherosclerosis occurred in the larger vessels.

5] Severe fibrosis of these smaller arteries was twice as frequent in patients with hypertension or cardiac enlargement. Other somatic diseases were apparently not etiologically concerned in this process.

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Spinal extradural cysts

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In 1934, Elsberg, Dyke, and Brewer[3] reported on 4 patients with extradural cysts in the dorsal region of the spinal neural axis. Upon analysis, these lesions presented a definite syndrome described as follows:

"The individual is in adolescene with the history and symptoms of progressive spastic paraplegia. Pain is absent or is not a prominent symptom. The objective disturbances of sensibility are slight, and their upper level is in the mid-thoracic region, usually the 6th or 7th thoracic dermatome. Manometric tests demonstrate a subarachnoid block with the characteristic spinal-fluid changes of cord compression. Measurements on antero-posterior X-ray films show that the interpeduncular space of three or more vertebrae somewhere between the 4th and 9th thoracic vertebrae are enlarged. Pedicles of the affected vertebrae, especially those of the 6th, 7th and 8th, are narrowed and atrophic."

In 1935, Lehman[4] added several other points to the syndrome as outlined by Elsberg and associates. These included: [1] epiphysitis involving the bodies of the vertebrae in the region of the lesion with the development of a marked kyphosis and [2] a marked variability in the signs and symptoms of spinal cord compression as compared to the steady progress of such symptoms and signs in cases of expanding neoplastic lesions.

Cloward and Bucy[6] discussed further the part that extradural cysts may play in the development of kyphosis dorsalis juvenilis. Cloward[7] emphasized that the cysts can also occur in adults and described cysts found in the lumbar area of the spinal cord. In 1942, Mayfield and Grantham[16] raised the question of whether trauma may or may not be an etiologic factor. In 1944, Good, Adson, and Abbott[17] described the first cyst to fill with Lipiodol at myelography.

The purpose of this paper is to add 7 more cases to the still limited literature about this subject, to review the pertinent literature, and to reevaluate both symptomatology and etiology in the light of this review and these new cases.

Case 1. A 29-year-old woman was admitted to the Duke Hospital on September 17, 1942. She had noticed four years previously an aching discomfort and a moderate amount of local swelling across the instep of her right foot. This pain occurred intermittently and lasted several days to several weeks; six months before admission, pain became constant. A month before admission, the patient began having pain in the lower lumbar region, the right hip and along the posterior aspect of the right thigh. This pain also became constant but was relieved slightly by recumbency. Pain was accentuated by sitting, standing, or walking. At this time, she noticed progressive weakness of the right leg and had to walk on her toes.

Neurologic examination at admission revealed the right ankle jerk and right knee jerk to be diminished slightly as compared to the left. The patient had atrophy of her right calf which measured 2 cm. as compared to the left. Definite hypesthesia and hypalgesia were found over the dermatomes from L2 to S1. Roentgenograms of the lumbar spine in various views were essentially negative. Manometric examination was normal, and the total protein of the spinal fluid was 29 mg. per cent per 100 cc. Lipiodol studies showed no definite defect in the spinal subarachnoid space.

The patient was readmitted to the hospital on December 6, 1943. All her symptoms—including pain in the right ankle, knee, and hip, and weakness of this extremity—had progressed. She had also noticed some numbness along the lateral aspect of the calf extending into the big toe in her right foot. When lying flat, the patient was unable to dorsiflex her foot but could dorsiflex her toes. The pain was constant and was not accentuated by coughing, straining, or sneezing. She never had had any involvement of the left leg and noticed no urinary disturbance.

Examination revealed the following positive findings. The entire right lower extremity had obvious atrophy. The right thigh measured 3 cm.

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Fig. 1. Drawing of the extradural cysts encountered at operation in Case 1

smaller than the left, and the right calf was 2 cm. smaller than at corresponding levels on the left side. All muscles of her right foreleg were extremely weak, and she was unable to dorsiflex the foot or toes or to evert the foot. She walked on the ball of her right foot with the right knee and hip slightly flexed. Marked hypalgesia and hypesthesia occurred over the dermatomes of L4 and L5 on the right side and, to a lesser degree, over those of L2 and 3 and S1. The right knee jerk was decreased and the right ankle jerk was absent. Tenderness was found on deep pressure over the spinous processes of L3, 4, and 5. Anterior flexion of the spine was limited to 45 degrees, producing pain in the right hip. Straight-leg raising was limited, and Lasègue's sign was positive on the right. Neither cerebrospinal fluid studies nor Lipiodol examination was carried out at this time. X-rays of the lumbar spine disclosed that the pedicles of L2 and L3 were spread and the right inferior pedicle at L4 was thinned.

The diagnosis of ruptured intervertebral disk or cauda equina tumor was made, and operation was advised. The fourth and fifth lumbar interspaces on the right side were explored. No abnormality was encountered. A partial hemilaminectomy at L4, a complete hemilaminectomy of L3, and a partial hemilaminectomy of L2 and L1 were then performed, exposing 4 extradural cysts.

The largest cyst measured 4 cm. in length by 2 cm. in diameter and extended from the upper edge of the lamina of L4 to the upper edge of the lamina of L3 and along the right posterolateral aspect of the dura mater. The upper edge of the cyst was attached to the dura by a small pedicle 2 by 3 mm. in diameter. The wall of the cyst was extremely thin and contained clear fluid which communicated with the subarachnoid space. The cyst displaced the dural sac to the left and forward and, after several small fibrous bands were sectioned, was separated from the sac without difficulty.

When the dura was incised in elliptical fashion about the neck of the cyst, the arachnoid was found to be continuous with the cyst wall. The next largest cyst, which measured 2 by 1.5 cm., extended from the upper edge of the lamina of L3 to beneath the lamina of L2 and along the posterolateral aspect of the dura on the right. The cyst's point of attachment was exactly in the midline and the shape and structure were similar to the first cyst. This cyst also communicated with the subarachnoid space.

A third cyst was encountered in the first lumbar interspace and only protruded posterior to the dura for several millimeters. This cyst was 2 to 3 mm. in diameter. A fourth and still smaller cyst, or dural defect, was found at the third interspace in the midline of the posterior aspect of the dura. This cyst appeared as a tiny dural defect 2 mm. in diameter through which the arachnoid bulged for a distance of perhaps 1 mm. (Fig. 1).

Pathologic examination of the cyst showed that the wall was made up of a thin layer of hyalinized, collagenous connective tissue which contained almost no cellular elements. In some places, tiny oval structures made up of arachnoidal cells were found, suggesting the structure of an arachnoid body or granulation. No evidence of an epithelial lining was seen.

Comment. Because the cyst originated in the lumbar canal, this case varies from the usual syndrome reported by Elsberg. Pain was the outstanding complaint and seemed definitely related to positional changes. The cysts were multiple with their points of origin not related to the nerve roots, but near the midline of the posterior dural envelope.

Case 2. A 43-year-old woman was admitted to the Duke Hospital on November 5, 1943. About seven years prior to admission, the patient had onset of recurrent attacks of low sacral pain which radiated down the back of both legs into her feet. About the same time, she noticed irregular, recurrent, and bilateral lower abdominal pains which were worse during menstruation. With this ab-

dominal pain, she had some vaginal pain and burning.

She had noticed recurrent stiffness and weakness of both lower extremities two years before admission. These symptoms were more marked on the left and were associated with a burning sensation in both feet; at times, her feet dragged. In the year before admission, she had difficulty initiating micturition and had episodes of short-lived, bladder paralysis. Bilateral, lower abdominal pain would appear with such voiding difficulties, but no rectal sphincter disturbance occurred. Shortly before admission, weakness and stiffness of the left leg and associated lumbosacral pain had progressively increased.

Examination revealed a mild dorsal kyphosis and tenderness to percussion over the spinous processes of the ninth and tenth thoracic vertebrae. Marked weakness and some spasticity were found in both legs but were more severe on the left. Perception of vibration was lost below the level of the iliac crest on the left and below the ankle on the right side, but position sense, light touch, and pinprick modalities were intact. The lower superficial abdominal reflexes were absent, the knee and ankle jerks were hyperactive; the left knee jerk was more hyperactive than the right. Bilateral, sustained ankle clonus was observed, and the Babinski sign was present bilaterally.

X-rays showed that the pedicles on the right side in the midthoracic region were not as sharply outlined as those on the left, but this was thought to be secondary to a slight rotatory scoliosis. Some calcification of the intervertebral disk between T10 and T11 was noted. A lumbar puncture revealed clear spinal fluid with a protein content of 64 mg. per cent per 100 cc. Manometric study showed a partial block. A Pantopaque myelogram showed a block with a curved defect at the T11 interspace. Cystometrograms disclosed an atonic bladder.

A thoracic laminectomy was performed on November 16, 1943. Upon removing the spinous process and laminal arches of T11, normal dura was noted caudally but in the midportion of the exposure was found a thin-walled, smooth, cystic structure filled with clear fluid which resembled cerebrospinal fluid. The laminectomy was then carried up to the caudal portion of T9. The laminal arches in this area were markedly thinned out. The cyst was easily dissected from the dorsal dura but was ruptured in this procedure. At the level of T9, the cystic structure encircled the dura bilaterally. A catheter was passed upwards within the cyst for a distance of over 6 cm., and the cavity was thought to extend up to T6. Only the lower end of the sac was removed, because further extension of the laminectomy was not indicated.

Microscopic examination of the tissue showed that it was composed of loosely arranged fibrous tissue with a minimal infiltration of round cells. No definite cyst wall could be identified in the sections, but, in 1 area, the tissue was oriented in 2 layers of connective tissue—a layer made up of dense fibrous tissue and a layer of more loosely arranged connective tissue. These layers could conceivably represent dura and arachnoid.

The postoperative course was uneventful, and examination on October 10, 1944, found the patient free of back pain with normal and equal reflexes in the lower extremities.

Case 3. A 50-year-old man was admitted for the first time on December 4, 1939. The patient had been struck across the right side of the head and across the base of the cervical spine by a falling tree twenty-eight years prior to admission. Upon recovering consciousness, he had noted loss of sensation in the fifth finger and along the medial aspect of the fourth finger on the right side. He also had some vague weakness in his hand.

He continued to have loss of sensation over the distribution of the dermatomes C8 and T1 on the right and some weakness of the intrinsic muscles of the right hand which are supplied by the ulnar nerve. The patient also had a vague pain in the forearm and hand which, in the ten years prior to admission, had decreased in severity, but which, in the six months before admission, had become worse and had become almost unbearable. The pain was increased with change of neck position. In the year before admission, he had had a sharp, stabbing pain in the left heel. He had bladder hesitancy, periods of temporary bladder paralysis, and loss of libido and potency.

Examination revealed slight atrophy of the thenar eminence with mild clawing of the hand. He had weakness of the lumbricals and interossei; hypalgesia and hypesthesia in the C8, T1, and T2 dermatomes; loss of position and vibratory sensation in the fifth finger; slight hypalgesia over the ulnar side of the left forearm; and an area of hypalgesia about both breasts. The left knee jerk was decreased as compared with the right, and an extensor plantar response was seen on the right. He had a dilated, fixed, and irregular left pupil, a small right pupil, right enophthalmos, and slight right ptosis.

X-rays revealed narrowing of the interspaces between the sixth and seventh cervical vertebrae and osteoarthritis and questionable narrowing of the interspace between the seventh and eighth vertebrae. Marked bony proliferation was found along the anterior margin of these vertebrae with some attempt at bony bridging. A lumbar puncture showed a normal subarachnoid pressure and normal manometric studies. The spinal fluid protein was 46 mg. per cent per 100 cc.; Kahn, 4 plus; and colloidal gold curve, 4 4 4 4 3 2 1 1 1 0. A chest film revealed an enormously widened aorta consistent with syphilitic aortitis.

The patient was discharged on December 8, 1939, with the diagnosis of systemic and central nervous system syphilis.

He was readmitted on April 11, 1944, with severe pain beginning in the right shoulder and radiating down the posterolateral aspect of the

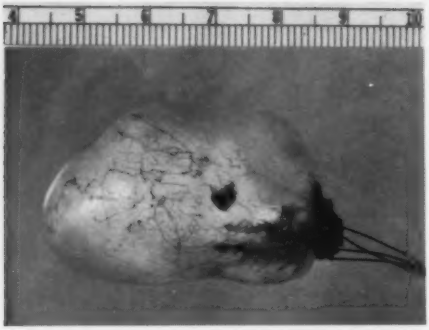

Fig. 2. Cyst removed from Case 4. The sutures are attached to the pedicle.

arm through the ulnar portion of the forearm, and into the middle finger and medial one-half of the ring finger. He had numbness in the same area and burned himself on that arm without knowing he had done it.

Examination showed definite atrophy of the hypothenar eminence, hypalgesia in the forearm, and anesthesia of part of the hand. The right ankle jerk was decreased. Pupillary changes were still present.

X-rays of the cervical spine again revealed extensive arthritis of the lower 3 cervical vertebrae and large bony bridges along the anterior margins of the vertebrae.

A laminectomy was performed and, upon removing the lamina of C7, an extradural, arachnoidal cyst was encountered lateral to the dura and extending from the upper aspect of the lamina of C7 to the upper aspect of the lamina of T1. The cyst was 4 cm. long and 1 cm. in diameter and was attached to the dura along its anteromedial aspect for a distance of 2 cm. The eighth cervical nerve root on the right was pushed anteriorly. Removal of the cyst left an opening in the anterolateral aspect of the dura about 2 cm. in length. On the sixth or seventh postoperative day, the patient developed a dural leak which required a secondary closure of the dura.

At microscopic examination, the cyst was composed of hyaline and degenerative fibrous tissue resembling dura and had a lining of thickened arachnoid tissue. In one area, inflamatory cells had infiltrated.

He was seen five months later and still had arm pain when the weather was cold. The atrophy and sensory changes were unchanged. A chest x-ray revealed an aortic aneurysm, and he developed symptoms of early cardiac failure.

Comment. Here too, pain was the most prominent complaint. The onset of symptoms was associated with trauma, the sensory changes were marked, and the cyst originated from the anteromedial aspect of the cervical dura.

Case 4. A 13-year-old boy was admitted on November 12, 1952. The patient had stumbled and had fallen over his left leg three weeks prior to admission. He immediately noticed that his left leg was numb, stiff, and weak. These symptoms persisted until one week before admission when his right leg started to drag and became stiff and weak. He had intermittent, lower extremity numbness but no pain and no sphincter difficulty.

Examination revealed a paraparesis which was possibly more severe on the right. A small patch of hypalgesia was found over both anterior midthighs, but position and vibratory sensations were intact. The knee and ankle jerks were hyperactive bilaterally, and the Babinski sign was present on each side.

X-rays showed slight narrowing of the bodies of some of the thoracic vertebrae, but the changes were not typical of juvenile epiphysitis. The pedicles were widened at T8 and 9. A lumbar puncture revealed an incomplete block by manometric examination, and the spinal fluid protein was 52 mg. per cent per 100 cc. A Pantopaque myelogram showed a partial block at T8 with a meniscus sign. The oil was thinned out in this area, suggesting an extramedullary lesion.

A dorsal laminectomy was performed on November 14, 1952. With the exposure of the dura at T9, the lower border of a grayish extradural mass was disclosed which, with the removal of the spinous process and laminal arch of T8, was found to have depressed the dural sleeve to almost one-half its diameter. The lesion was a cyst which was attached to the dura by 2 small processes arising from the dura. The dural structures seemed to continue into these pedicles for a distance of about 2 mm. where the typical arachnoid structure of the cyst became apparent. These processes were divided between sutures, and the dura was closed separately.

Histologically, the specimen was made up of rather dense fibrous connective tissue containing few cells with longitudinally oriented parallel fibers. A few small blood vessels were in the outer wall, but no epithelial lining. Here, also, 2 layers made up the wall—1 more loosely arranged than the other—which could represent the dura and arachnoid.

Postoperatively, muscle strength significantly increased and sensory examinations were normal.

Comment. As in Case 3, the onset was associated with trauma.

Case 5. A 28-year-old woman was admitted on August 21, 1953. She was well until 1946 when, during her third pregnancy, she noticed the gradual onset of weakness in both legs. This improved after delivery but recurred just before her next pregnancy. She improved during this pregnancy, but, after delivery, her weakness recurred and was worse than before. This sequence was repeated

again in 1949 and in 1951, and, following the latter episode, weakness became progressive.

In April, 1953, she became too weak to walk. The right leg was more involved than the left. Both legs had a dull ache most of the time, and sitting caused hip pain. In the winter, her legs seemed to "stay cold and blue most of the time." She had difficulty knowing where her legs were and had to look at them when moving them. Her symptoms were worse with constipation which she had had frequently, and she stated that she had had urinary frequency and occasional incontinence since childhood.

Examination disclosed a profound global spastic weakness of both lower extremities with greater involvement on the right side. Proprioception and 2-point discrimination were absent in the lower extremities. Light touch was markedly decreased over the lower extremities, and vibratory sensation was absent below the level of T12. She had right patellar clonus and bilateral Hoffmann reflexes and Babinski signs. The superficial abdominal reflexes were absent.

X-rays of the thoracic spine showed almost complete erosion of the pedicles in the upper and middle thoracic areas. Evidence was found of an old traumatic injury in the midthoracic area, slight wedging of 1 vertebra, and roughening of the joint space between 2 adjacent vertebrae. A myelogram showed a partial block at T10 which extended up to T8. The spinal fluid protein was 85 mg. per cent per 100 cc.

A laminectomy was performed at T8, 9, and 10 revealing a semitransparent, cystic structure filling the entire dorsal half of the spinal canal and compressing the cord beneath it. The cyst was rounded at its lower end, and this end could easily be dissected away from the dura. At the upper pole, however, the cyst ended in a more densely adherent, fibrous attachment to the dura and a small projection of the cyst could be traced into the nerve root sheath of T8 on the right. About 1 cm. rostral to the cyst, the lower pole of a similar structure could be visualized; the laminectomy was extended and another cyst of about the same size and configuration as the first was uncovered extending up to T4.

This cyst was also dissected from below upward and was found to be attached at its upper pole to a posterior nerve root sheath on the left. Both attachments were divided between silver clips. At the level of approximately the T7 posterior root sheath on the right, and again at T11 and T12 on the right, small dome-like cystic structures were found, each less than 1 cm. across, arising from the posterior root sheaths. None encroached on the cord, and the cysts were not resected, but an operative note stated, "it was conceivable that they might develop into larger, pedunculated cysts at a later date."

Examination of the cyst disclosed a thin-walled cystic structure with a moderately vascularized, dense, fibrous tissue wall. A minimal infiltration

Fig. 3. Cyst reoved from Case 6

occurred with chronic inflammatory cells and no epithelial lining.

The patient was walking normally four months after surgery and had no bladder difficulty, although she still had some girdle pain.

Comment. Multiple cysts were found in this patient in the dorsal area arising from nerve roots. Sensory changes were prominent.

Case 6. A 46-year-old man was admitted on January 17, 1955. This patient was well until 1950, when he noticed occasional stiffness in his right ankle joint. On 2 or 3 later occasions, the ankle joint was swollen. From 1950 through October 1953, he gradually developed stiffness in all joints in the lower extremities and an increasing degree of weakness in both legs. He needed a cane for walking. In this same period, he had flexor spasms in the lower limbs. Since October 1953, the weakness, flexor spasm, and spasticity of both lower limbs had definitely increased, and he had numbness in both feet. About eighteen months before admission, he could walk only with great difficulty. His condition remained essentially unchanged throughout that time. He had no urinary difficulty or impotence and no pain. The patient had chronic constipation, however, and had had only 2 or 3 bowel movements a month since childhood.

Examination disclosed a spastic paraplegia in extension with a slight degree of extensor voluntary power and marked hyperactivity to noxious stimuli. Diminished to absent vibratory sensibility occurred from the iliac crest down, and postural sensibility was absent in the left foot and markedly decreased on the right. The deep tendon reflexes were bilaterally equal but hyperactive at the knees and ankles. A Babinski sign was present on the left. The patient had no deformities of the spine and no point tenderness upon palpation or percussion.

X-rays of the spine showed pedicle erosion at C7, 8, and 9, and a Pantopaque myelogram revealed complete block at T7.

Laminectomy was performed which disclosed a cyst overlying the dura from T8 to T10. The cyst

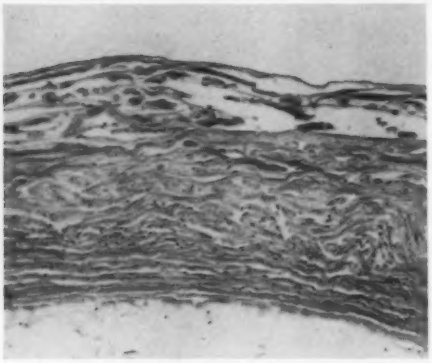

Fig. 4. Photomicrograph of the wall of cyst of Case 7. The wall is composed of fibrous and collagenous tissue (hematoxylin and eosin).

was as wide as the spinal canal and appeared attached at the exit of the posterior nerve root at T9. The cyst was easily separated from the underlying dura and divided at its neck. No communication was apparent with the subarachnoid space.

At microscopic examination, the cyst was composed of thick, fibrous connective tissue containing small blood vessels in its wall. In 1 section, 2 layers could be identified, 1 more loosely arranged than the other. The lining in some areas was composed of rounded cells, but elsewhere the cells were flattened or indistinguishable. Sections through the pedicle showed no evidence of communication with the subarachnoid space.

Postoperatively, the patient had precipitant urination and needed an indwelling catheter. A cystometrogram revealed a hypertonic, neurogenic bladder. At the time of discharge, he was able to walk with a cane, but, four months later, he still had extensor spasm of the right leg. Sensation had considerably improved.

Case 7. A 14-year-old boy was admitted November 8, 1956. Approximately eight weeks prior to admission, the patient hurt his left knee while playing ball. The knee hurt for several days, but the pain gradually subsided. He tripped and fell three weeks later while doing farm chores and reinjured his left knee. This pain did not subside and, in the next week, he had difficulty in flexing the knee as well as generalized weakness in the left leg. He experienced similar difficulty in his right lower leg four days prior to admission. The weakness progressed until he was unable to walk. In addition, he had some vague numbness in the left leg and, since the onset of weakness, slight hesitancy of urination and nocturia.

For several months his friends had noticed that both his legs were stiff, particularly when he ran.

Examination revealed marked weakness and spasticity of both lower extremities as well as weakness of the lower abdominal muscles. He had hypalgesia and hypesthesia to a level of T8 bilaterally. Position sense was impaired in both lower extremities. Vibratory sensation was absent to the iliac crest on the left and absent to the knee and impaired to the iliac crest on the right. In the upper extremities, his reflexes were generally hyperactive but equal. The left superficial abdominal reflexes were absent, and, although absent on the right, the lower abdominal reflex was present in the upper quadrant. The knee and ankle jerks were 4+ bilaterally, and he had bilateral extensor plantar responses. The cremasteric reflexes were absent bilaterally.

Thoracic spine films showed the interpedicular space to be widened and the pedicles to be eroded from T6 through T8. A lateral thoracic spine film revealed changes in the anterior portion of the vertebral bodies of T6, T7, and T8, typical of early kyphosis dorsalis juvenilis as described by Cloward and Bucy.[6] The spinal fluid contained a total protein of 95 mg. per cent. The subarachnoid space was found to be partially blocked by manometric studies and completely blocked during myelography at T8.

A thoracic laminectomy was carried out including D6, D7, and D8. Extradural fat was conspicuously absent, and, with the removal of the lamina of D8, an underlying cystic structure became apparent.

This cyst measured approximately 7 cm. in length and was attached by a pedicle through which there was communication with the subarachnoid space. The pedicle was attached to the origin of the dorsal root at T8 on the left. The entire cyst was removed without difficulty. Histologically, the specimen was made up of rather dense collagenous connective tissue which resembled dura.

At the time of discharge, the patient had no sensory deficit and was rapidly regaining the strength in his legs. He had no urinary difficulty.

DISCUSSION

Of 45 patients similar to these who have been studied from available source material, 27 were men and 18 were women; the sex of 1 was not indicated. The age distribution had the following pattern:

0-10	11-20	21-30	31-40	41-50	51 +
1	19	6	3	12	2

Spinal extradural cysts are common during adolescence, but the lesions are certainly not confined to this age period. In these patients, average duration of symptoms before operation was three and one-half years; duration varied between two weeks to twenty-eight years. Trauma seemed to be a precipitating

factor in 11 patients. In most instances, on examination, motor weakness was relatively more prominent than sensory changes. Despite frequent statements that pain is not common in this condition, pain occurred in 23 of the 45 patients and was severe in some and especially severe in patients with cysts in the cervical and lumbar areas. All of the patients with cervical, thoracolumbar, lumbar, and sacral cysts in this entire series had pain. Pain was less apt to be present with thoracic cysts. Bladder or anal sphincter involvement or both occurred in 15. Vasomotor or autonomic nervous system changes occurred in 6; both patients with cysts in the cervical area had Horner's sign. Peet and Kahn[5] have discussed in some detail the vasomotor phenomena seen in 1 of their patients with a thoracolumbar cyst.

X-ray studies showed changes in the vertebral column in 32 patients; erosion of the pedicles and widening of the spinal canal were most common, followed by increase in the anteroposterior diameter of the canal and vertebral body changes.

In 24 patients, a subarachnoid block was demonstrable by either manometric or myelographic examination. The spinal fluid protein was over 50 mg. per cent in 18 patients, and in all but 4 in which spinal fluid protein was increased an associated block of some degree was found by these special studies. In 1 of these 4 patients, neither manometric studies nor a myelogram was performed.

The cysts occurred predominantly in the thoracic area; 30 appeared in this location. Of the other cysts, 2 were cervical; 4, thoracolumbar; 6, lumbar; and 3, sacral. The cervical, lumbar, and sacral cysts—except for a lumbar cyst in a 20-month-old child—all appeared in patients 27 years of age or older. Only 1 of the 4 thoracolumbar cysts occurred in an adolescent. In other words, although this condition is relatively common in adolescents, usually the cysts occur in the dorsal area in the adolescent. Kyphosis occurred in 8 patients, 2 had wedge-shaped vertebrae by x-ray, and 1 was reported as being round shouldered. Kyphosis developed postoperatively in 3 additional patients. In 3, kyphosis became worse after operation, and, in 1 patient, scoliosis became worse after operation. In this regard, Lehman[4] states in his article that "kyphosis is not a common sequel of laminectomy in the absence of disease of the vertebrae." On the other hand, Shenkin[19] says that "the development of kyphosis postoperatively is not rare in young persons after dorsal laminectomies."

Cloward and Bucy[6] believe that kyphosis may progress postoperatively because [1] it is only natural to expect some further extension of the destruction of the vertebral body before healing can occur and [2] laminectomy and removal of the vertebral spines have lessened the resistance of the vertebral column to a compressing and flexing force. Cloward and Bucy also believe that the changes in the vertebral body which lead to kyphosis are the result of cyst pressure on the epidural veins which drain these structures, causing hyperemia and venous stasis in the vertebral body and changes in the bone. They feel that the hyperemia and venous stasis must occur in growing vertebrae and that "if symptoms of cord compression begin after bony development of the vertebral column is complete, the changes of kyphosis dorsalis juvenilis do not occur."

Contrary to this, 4 of the 8 patients with kyphosis were over 28 years old and all 4 noted onset of their symptoms after adolescence. An additional 42-year-old patient was said to have been round shouldered and had x-ray abnormalities similar to those of kyphosis dorsalis juvenilis. This patient had onset of her symptoms at 32.

In many instances, the case reports do not indicate whether the cysts communicated with the subarachnoid space or not, but a definite affirmative statement can be made in at least 12 cases and, as has been pointed out by others, this communication probably accounts for the rather marked variability and fluctuation in symptoms demonstrated in these patients.

In our Cases 1, 3, and 5 and in 4 others, the symptoms were also affected by changes in position. In 8 patients, including our Case 1, symptoms fluctuated with an associated communication with the subarachnoid space. In 2 patients, symptoms fluctuated but no such communication occurred. This change or variability in symptoms was possibly far more frequent than the above figures would indicate, because many of the histories in the literature were short or incomplete.

The prognosis would seem to be good for those patients who are operated upon—20 were essentially cured and 10 incompletely cured.

An examination of the above data reveals that the syndrome as presented by Elsberg, Dyke, and Brewer should be altered to include the occurrence of extradural cysts [1] in areas of the spinal canal other than the thoracic region, [2] in patients who are beyond adolescence, and [3] in patients who may have pain as a prominent symptom. Other writers have stated that the syndrome usually occurs in boys and that bladder involvement is unusual. Neither of these statements appears to be true.

Rexed[21] made microscopic sections of human spinal nerves and nerve roots and found a "more or less intense proliferation of the root arachnoidea" which was, in some cases, connected with cysts in the roots themselves. He found these proliferative changes not only in the roots but also in the dense dural sheath surrounding the roots and thought they were due to a developmental disturbance. Of 17 patients, 8 showed this change in Rexed's series. Conceivably, if these cystic changes can occur in the dura around the roots, they can also occur elsewhere in the dura where cysts may lie dormant unless communication is established with the subarachnoid space where the pulsatile, hydrostatic pressure of the cerebrospinal fluid can act to enlarge the cyst. In Strully's second case,[30] additional small cysts were found within the nerve roots at the level of the larger lesion.

The extradural cysts discussed in this paper are not to be confused with the perineurial cysts described by Tarlov[23] which are fusiform, multiloculated cystic structures appearing in the roots and containing nerve fibers. Cysts may well arise, however, from the same proliferative and cystic changes described by Rexed.

Frequently, the patient's difficulty seemed to be precipitated by trauma. To assume that the trauma caused the herniation per se is unreasonable; more likely, the sudden pressure changes associated with the trauma were sufficient to make clinically apparent a large, slow-growing, and possibly self-emptying cyst which had been present for a long time.

Several authors[20,23,27,30] have reported the postoperative occurrence of extradural cysts from a true herniation of the arachnoid through a dural defect incurred at the time of removal of cord tumors and ruptured intervertebral disks. These are traumatic extradural cysts and different from those reported in this paper which are assumed to be congenital. However, in 2 of the patients with trauma prior to onset of symptoms, Meredith[12] and Mayfield[16] found old hemosiderin deposits in the wall of the cyst; in the case of Meredith, in addition to the hemosiderin, a piece of necrotic bone was found which was not related to the laminectomy. Possibly, trauma may have had a more direct effect in these cases.

The fact that these extradural cysts are more frequently found in the lower part of the spinal canal where the hydrostatic pressure may be the greatest supports the impression that this pressure may play a role in the development of the cyst.

The cyst must enlarge very slowly because of the disproportion between the large size of the cyst and, often, the lack of symptoms. The fact that the cyst may be able to empty itself by way of its communication with the subarachnoid space would also permit the sac to enlarge without producing much in the way of symptoms. This would progress to the point where cord compression became clinically evident because of size alone, or because a space-occupying lesion developed due to intermittent occlusion of the pedicle.

If, as Cloward and Bucy[6] believe, the bone changes leading to kyphosis must occur in growing bone, the occurrence of kyphosis in an older patient with this condition would indicate the lesion had been present at least since adolescence. There were 3 patients—counting Cohen's patient with coexisting tumor—aged 48, 32, and 43, who had kyphosis and who had onset after adolescence. This is a further argument that these lesions may be longstanding, slowly expanding, possibly congenital cysts which may be asymptomatic until cord compression occurs. Also, in favor of a congenital basis for the cysts are their multiple occurrence and the finding of a cyst in a 20-month-old baby.

If cysts may be quite large before producing symptoms and then, at times, only follow trauma, the cyst may be present without producing signs or symptoms. This was true in

the third case of Strully[30] in which the patient had a ruptured disk, the removal of which relieved her pain. The cyst was an incidental finding and was not removed at operation.

It is of interest that, with the exception of the cyst in the lumbar area in the 20-month-old baby, all of the cervical, lumbar, and sacral cysts occurred in individuals 27 years of age or older and, with the same exception, all the 23 patients under the age of 27 had their cysts in the thoracic or thoracolumbar area. Only 2 were in the thoracolumbar area. Many of the older patients did have thoracic cysts, but the above data would indicate that, when the cysts occur in the thoracic area, they tend to produce symptoms earlier. This is no doubt due to the fact that a lesion in the thoracic canal is more likely to be symptomatic because of the narrowness of the spinal canal in this region.

In his original paper, Elsberg[3] offered the possibilities that these cysts were either a "congenital diverticulum of the dura mater" or a "herniation of the arachnoid through a congenital defect in the dura mater." Primarily because of the histologic similarity between the cyst wall and the dura, most writers since that time have accepted the former idea. The cysts at this hospital were all histologically similar to dura or to a membrane made up of both dura and arachnoid. The possibility that the membrane arose from the arachnoid and became thickened and altered during the period of enlargement could not be excluded, however, on the basis of the microscopic features.

In 27 of the patients in the total series, the pathologic description was consistent with the diagnosis of a dura-like membrane. In fact, in 16 of these patients, it was stated specifically that the cyst wall had the morphology of dura. On the other hand, in only 4 patients was the cyst described as resembling arachnoid tissue; in 3 of these patients, the cyst was midline. Cloward and Bucy[6] state that the cyst is probably an evagination of both dura mater and arachnoid which, under the influence of the intracystic pressure, has fused into 1 membrane. A collagenous wall of the thickness seen in these cysts is foreign to the structure of the arachnoid but quite comparable to the dura mater.

There seem to be 3 sites on the dura where these cysts are apt to arise: [1] from the dural sac (these are the midline cysts and 11 cysts in the total series had their point of origin in or near the midline); [2] from an attachment to the dural sleeve at its origin from the dural sac, usually on the posterior roots (in 20 patients, the cyst seemed to be attached here); and [3] in the dural sleeve itself (the two cysts in O'Connell's case[28] occurred at this point).

SUMMARY

The literature on spinal extradural cysts is reviewed and 7 more cases added to the 38 already reported. The patients with this condition usually present a long history of intermittent difficulty. The lesion is large and probably caused by a longstanding defect, possibly congenital, which enlarges slowly, empties itself, and allows for accommodation until the cyst becames clinically apparent as a result of pressure changes which are sometimes associated with trauma or occlusion of its pedicle.

These cysts are found most often in the thoracic area where they produce symptoms earlier and may be associated with kyphosis dorsalis juvenilis.

For the cysts to cause pain is not unusual, especially if the cysts occur in the cervical, lumbar, or sacral areas.

The cysts may arise from proliferative and cystic changes in the roots and dura and probably are formed from the enlargement of these cysts by the pulsatile, hydrostatic pressure of the spinal fluid.

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Effect of ischemia on cyanide encephalopathy

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A PREVIOUS STUDY has shown that exposure of rats to hydrogen cyanide vapor under controlled conditions produces a high incidence of lesions of gray and/or white matter.[1] Distribution of the lesions depended in part on the size of the rat and depth and duration of the intoxication. Two observations suggested that the histotoxic effects of cyanide on gray matter might be potentiated by ischemic or anoxic anoxia: [1] unilateral lesions of cerebral cortex and corpus striatum were observed occasionally, suggesting a vascular factor, and [2] lesions of gray matter usually occurred after deep intoxication attended by some degree of respiratory and cardiac depression. To test this possibility, lesions were induced by cyanide in rats with cerebral ischemia due to unilateral carotid ligation. This maneuver greatly influenced the distribution of gray matter lesions, with far less effect on white matter lesions.

MATERIAL AND METHODS

Unilateral ligation of the common carotid artery was performed under pentobarbital anesthesia in 24 female albino Wistar rats; half of the animals weighed an average of 225 gm., and half weighed an average of 160 gm. In each weight group, half the ligations were on the right and half were on the left side. Care was taken to separate the nerve attached to the artery, but, occasionally, injury to the nerve resulted in unequal palpebral fissures. Although brain lesions are not produced by ligation alone,[2] the blood supply to the corresponding cerebral hemisphere is reduced. On the day after ligation, the rats were exposed to hydrogen cyanide for twenty-five to thirty-five minutes in individual jars. The technic of exposure was that described previously,[1,3] except that a healthy, unligated rat accompanied the ligated rat in each jar and 3 rather than 6 jars were handled simultaneously. Placing 2 rats in each jar complicated the exposure because of individual variations in susceptibility to cyanide. The exposure was conducted according to the reactions of the ligated rat, even when this neglect of the control rat led to death.

The survivors were sacrificed two to four days after exposure. The brains were fixed in acetate-buffered 10% formalin and cut in 2- or 3-mm. blocks. Paraffin sections were stained by the hematoxylin-eosin and Luxol fast blue–periodic acid–Schiff methods. Many blocks were cut in subserial sections. The eyes also were studied histologically, but no lesions were found.

RESULTS

Mortality during exposure. A total of 3 ligated and 7 control rats died during or immediately after exposure. This was not taken to indicate that ischemia protected against cyanide poisoning because the conduct of the exposure favored the survival of the ligated animals. Evidently, ligation had no major influence on the immediate mortality. In some instances, the ligated rat actually appeared more severely affected; in a few cases, the opposite was true, and, occasionally, the relative intoxication in a particular jar reversed during exposure.

Incidence of lesions. No lesions were observed in the ligated or control rats that died during or immediately after exposure. Each of 21 ligated and 15 of 17 control rats that survived exposure but died within two days or

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Fig. 1. Homolateral necrosis of the cerebral but not the cingular cortex. The callosal radiation is edematous but not demyelinated. Two days after exposure. (Hematoxylin-eosin, × 17)

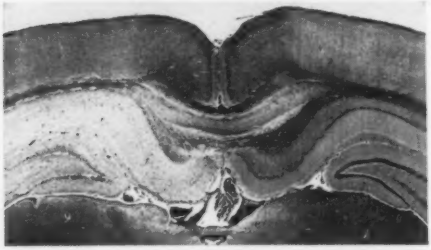

Fig. 2. Homolateral necrosis of hippocampus, with sharp midline demarcation from normal contralateral hippocampus. In contrast, the demyelinating lesion of the callosum is quite symmetric. Four days after exposure. (Hematoxylin-eosin, × 17)

were killed thereafter had lesions. The 2 controls that did not have lesions had inadequate exposures because the excessively deep intoxication of the ligated rats in the same jars necessitated premature cessation of cyanide. These results confirm the claim that the present method of administering hydrogen cyanide induces lesions in all or almost all survivors.[1]

Lesions of gray matter. The neocortex (Fig. 1), pyriform cortex, hippocampus (Fig. 2), substantia nigra, thalamus, and corpus striatum were involved in 20 of the 21 ligated rats with lesions. Several of these structures, in various combinations, usually were affected together. Extent of the lesions ranged from patchy selective neuronal necrosis to broad areas of total tissue necrosis. These lesions have been described and illustrated elsewhere.[1] The small rats had more lesions of the gray matter, especially the cortex, than the large rats; the reverse was true of white matter lesions.

Lesions of the gray matter were localized to the side of the carotid ligation. This is shown in Table 1, where the lesions have been classified as exclusively homolateral, asymmetric but predominantly homolateral, or symmetrically bilateral. Slight differences in the extent of bilateral lesions have been ignored; such lesions have been classified as bilateral.

The greatest tendency toward homolateral localization was observed in neocortical and thalamic lesions. Lesions of the pyriform cortex and gray matter of the striatum also were localized homolaterally; the similarity in the figures for these 2 structures reflected the fact that both often were injured together. The hippocampus was the area of gray matter least affected by carotid ligation, but, even here, half of the lesions had partial or complete homolateral localization. In several instances, the sharp midline demarcation between homolateral necrotic and contralateral intact pyramidal neurons attested to the lack of collateral circulation between the 2 hippocampal formations (Fig. 2). Homolateral lesions of the substantia nigra also were common, but no figures have been given because serial rather than subserial sections are required to evaluate small lesions in this structure. In 1 ligated rat, a contralateral lesion of striatum was associated with bilateral hippocampal and nigral lesions; the reason for this anomaly is not known.

Controls. The results presented above are clearly due to carotid ligation, since localization was homolateral in all but 1 animal. These results were compared with the incidence of unilateral lesions in nonligated rats.

In the control group, 1, several, or all of the gray matter structures listed above were involved in 9 of 15 rats with cyanide-induced lesions. Of these 9, only 1 had unilateral lesions of the cortex and hippocampus and another had an asymmetric, predominantly unilateral lesion of the striatum.

Although the difference between ligated and control rats was striking, the number of controls with gray matter lesions was small. Therefore, the previously described series of 155

TABLE 1

INCIDENCE AND DISTRIBUTION OF LESIONS AMONG 21 RATS EXPOSED TO HYDROGEN CYANIDE AFTER LIGATION OF 1 COMMON CAROTID ARTERY

	Exclusively homolateral	*Asymmetric but predominantly homolateral*	*Symmetrically bilateral*	*Totals*
Neocortex	8	2	2	12
Pyriform cortex	5	4	3	12
Hippocampus	6	2	8	16
Thalamus	3	1	–	4
Striatum (gray)	6	3	3	12*
Gray matter:				
Totals	28	12	16	56
Per cent	50%	21%	29%	100%
Striatum (white)†	–	1	6	7
Callosum	–	–	8	8
Callosal radiation	4	–	5	9
White matter:				
Totals	4	1	19	24
Per cent	17%	4%	79%	100%

*Not included in this figure was 1 rat with a contralateral lesion.

†Only lesions selective for white matter were included in this category.

rat brains with cyanide-induced lesions[1] was used for control purposes. The slides were reviewed, and cortical lesions were classified as unilateral, predominantly unilateral, and bilateral. Only the cortical lesions were studied because the large size of the cortex and lesions minimized chance for error, even without subserial sections.

Table 2 shows that cortical lesions were completely or predominantly unilateral in 25% of controls, as contrasted with 79% of ligated rats in Table 1.

Lesions of white matter. Of the 21 ligated rats with lesions, 11 had demyelinating lesions of the corpus callosum (Fig. 2), callosal radiation, white matter of the corpus striatum (Fig. 3), ventral hippocampal commissure, and anterior commissure. The other 10 animals, which, as a rule, were smaller, had damage to the white matter of striatum, but this was part of necrotic lesions that destroyed gray and white matter together; such cases were categorized in Table 1 only under the heading of "Striatum (gray)." In this section and in the lower half of Table 1, lesions of the striatum were included only when selective for the white matter.

As seen in Table 1, little effect was produced by ligation on the distribution of lesions that were selective for white matter. Lesions of the callosum, all of which were symmetric (Fig. 2), were observed in 8 rats. There were 6 rats with bilateral symmetric, selective damage to the white matter of the striatum (Fig. 3); 1 rat with homolateral predominance; and none with a unilateral lesion in this structure.* Symmetric lesions of white matter sometimes occurred in the same animals that had unilateral lesions of gray matter (Figs. 2 and 3).

The callosal radiation also appeared relatively resistant to the effects of ligation. Frequently, the callosal radiation was completely normal or showed nothing more than edema, even though the contiguous cortex, striatum, and hippocampus were necrotic. However, 2 rats had small, homolateral areas of demyelination associated with pyknosis of the oligodendroglial nuclei, contiguous with necrotic cortex (Fig. 4). In 2 others, extensive demyelination of the homolateral radiation was associated with necrosis of the gray matter of the striatum and cortex. In 5 rats, extensive, bilaterally symmetric demyelination of the radiation occurred, with no necrosis of the striatum or cortex.

A homolateral lesion of the anterior commissure, contiguous with an extensive zone of necrosis involving the corpus striatum, was observed in 1 rat (Fig. 5). Another had a symmetric zone of demyelination of the ventral hippocampal commissure.

Controls. The white matter was damaged

*Recently, some unilateral white matter lesions of the striatum have been produced by exposing rats to hydrogen cyanide shortly after carotid ligation; the ischemia was probably more severe because the short interval prevented development of collateral blood flow.

TABLE 2

INCIDENCE AND DISTRIBUTION OF CORTICAL LESIONS AMONG 155 NONLIGATED RATS WITH CYANIDE-INDUCED LESIONS

	Exclusively unilateral	*Asymmetric but predominantly unilateral*	*Symmetrically bilateral*	*Totals*
Neocortex	6	3	29	38
Pyriform cortex	10	3	38	51
Totals	16	6	67	89
Per cent	18%	7%	75%	100%

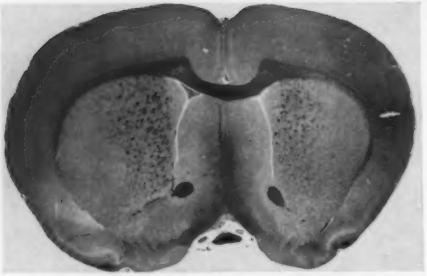

Fig. 3. Bilateral and symmetric demyelination of the lateral corpus striatum. Same rat as in Fig. 2. (Luxol fast blue–periodic acid–Schiff, × 9)

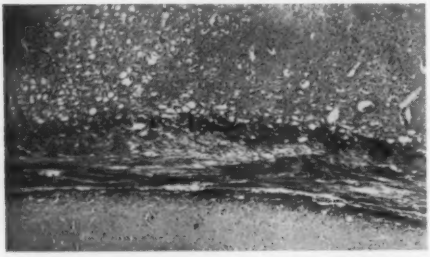

Fig. 4. Small area of demyelination in callosal radiation contiguous to necrotic cortex. Note fenestration of white matter and pyknosis of oligodendroglial nuclei. One day after exposure. (Luxol fast blue–periodic acid–Schiff, × 60)

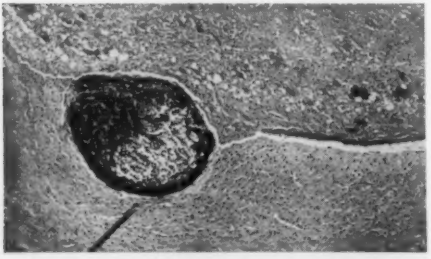

Fig. 5. Demyelination of portion of anterior commissure contiguous to necrotic corpus striatum. The ependyma (horizontal line of cells on right) separates necrotic striatum (above) from intact septum (below). Same rat as in Fig. 4. (Luxol fast blue–periodic acid–Schiff, × 60)

selectively in 14 of 15 controls with cyanide-induced lesions. All the lesions of the callosum and white matter of the striatum were symmetric bilaterally. Of 3 lesions of the callosal radiation, 1 was unilateral and associated with predominantly unilateral damage to gray matter of striatum.

In the larger control series, unilateral lesions of white matter also were extremely rare.

DISCUSSION

The results show that carotid ligation caused homolateral localization of cyanide-induced lesions of the gray matter. This probably was due to the additive effects of ischemic and histotoxic anoxia on gray matter, which has a high metabolic demand for oxygen. It is likely that the unilateral cyanide lesions that appeared in low incidence in nonligated rats had the same basis—namely, a retarded blood flow to 1 hemisphere due to the position of the head or neck or inherent anatomic factors. These results also lend some indirect support to the previously made suggestion that ischemic or anoxic anoxia consequent upon cardiac and medullary depression in deep cyanide intoxication may be partly responsible for bilateral gray matter lesions, especially those of the cortex, in nonligated animals.[1,4]

The most interesting result of the present study is the discrepancy between the reactions of gray and white matter lesions to ischemia. Homolateral lesions of white matter appeared after carotid ligation but usually were associated with homolateral necrosis of contiguous gray matter: striatum white matter with striatum gray matter, callosal radiation with contiguous striatum gray matter and cortex (Fig. 4), and anterior commissure with contiguous striatum gray matter (Fig. 5). In rats with selective damage to the white matter of the striatum or callosum, distribution never was completely homolateral. This fact is in accord with the rarity of unilateral lesions of white matter in nonligated rats.

The callosum, however, is a midline structure close to the potential source of collateral blood flow, and no evidence that unilateral ligation actually reduced its blood supply could be found. In fact, the homolateral cingular gyrus, which is contiguous with the callosum dorsally, probably had no loss of

blood supply because it almost always was spared despite extensive cortical necrosis (Fig. 1). (The homolateral cingular gyrus also was spared in nonligated animals with bilateral lesions, probably because of its close relationship to the anterior cerebral arteries.) Therefore, the actual effect of ligation on the blood supply of the callosum is uncertain.

No such uncertainty exists with respect to the striatum. The diminution of blood flow in this structure after carotid ligation was proved by administering nitrogen, which resulted in infarction of most of the homolateral hemisphere, including the striatum. Cyanide frequently caused homolateral necrosis of both the gray and white matter. However, 6 of the 7 selective white matter lesions were symmetrically bilateral despite ligation, and only 1 had a slight tendency toward homolateral predominance.

If ischemia potentiates the histotoxic effect of cyanide on sensitive areas of gray matter, why does it not potentiate the effect on sensitive areas of white matter? Possibly, under the conditions of exposure compatible with survival of the test animal, the cyanide concentration in sensitive areas of white matter inhibits oxidative metabolism to the extent that added anoxic factors have no further effect. However, in gray matter, the inhibition may be incomplete due to the higher concentration of cytochrome oxidase or cyanide-insensitive metabolic pathways; therefore, the added burden of ischemia or anoxic anoxia may determine the occurrence of necrosis. However, this mechanism would not account for the facts that [1] different areas of white matter vary in sensitivity to cyanide and [2] ischemia did not increase the sensitivity of normally insensitive areas. Following ligation, decreased blood flow to the homolateral hemisphere is accompanied by decreased delivery of cyanide; perhaps bilateral lesions (white matter) occur when these factors balance each other, but homolateral lesions (gray matter) occur when the former outweighs the latter.

SUMMARY

Unilateral ligation of the common carotid artery before exposure of rats to hydrogen cyanide vapor caused decided homolateral localization of gray matter lesions, with little effect on selective lesions of the white matter. The mechanism of cyanide action is discussed in the light of these findings.

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Function of astroglia in the water-ion metabolism of the central nervous system

An electron microscope study

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STRUCTURAL ANALYSIS of the central nervous system with so-called selective histologic technics is hindered by the fact that only partial views of the total organization are obtained. Thus the methods for the demonstration of astroglia, oligodendroglia, microglia, myelin sheaths, Nissl substance, and so forth emphasize only one component at a time and do not permit a spatial integration of all structural elements. On the contrary, with the electron microscope, all these and other components can be visualized simultaneously in thin sections fixed in osmium tetroxide and can be followed in their topographic relationships down to dimensions beyond the resolving power of the optical microscope. With this technic, the different types of glial cells that exist in the central nervous system may be recognized by their morphology, and their relationships with neurons, nerve fibers and endings, and so forth can be clearly determined.[1–4]

Since the first electron microscope observations on sections of the central nervous system, it has been found that the glial elements fill all intervening spaces between the neurons and the vascular elements and that no real extracellular spaces are present within the central nervous system.[5–8] The plasma membranes of all cellular components of the nervous tissue are in intimate contact with themselves and with the basal membranes of the capillaries. A distance of only 120 to 250 Å can be observed between the adjacent membranes, and this is filled by a material of definite electron density.[9] These facts completely contradict many physiologic observations that indicate the existence of a definite extracellular space in the central nervous system.[10]

From the structural viewpoint, it remained to be proved whether a true extracellular space may appear in experimental conditions leading to a surcharge of fluids and ions within the brain or whether the increased volume is due to swelling of one or more of the cell types present in the central nervous system.

In recent electron microscope observations, the ultrastructure of the oligodendroglial cells has been studied in detail and the role of these cells in central myelination has been demonstrated.[3,4] The structural characteristics and function of this cell type did not indicate a possible role in the water-ion metabolism of the brain. On the contrary, astroglia showed such a low electron density of the cytoplasm, in addition to its intimate relationship with the capillaries and the pial membrane, that it seemed worthwhile to investigate its possible participation in the water-ion exchange within the central nervous system. The working hypothesis was assumed that, in the brain, astroglia functions as a water-ion compartment replacing extracellular space of other tissues.

This hypothesis was tested by a series of in vivo experiments leading to a considerable increase of the general extracellular space of the body. As will be described, these drastic conditions did not result in an increase of the water content of the brain, and the structure

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of the glia cells remained unchanged. This problem was then approached more directly. It has been recently demonstrated that, by proper treatment in vitro with an isotonic physiologic solution, considerable swelling of the nerve tissue occurs. This has been interpreted as due to an increase of the so-called "extracellular space."[11,12] Essentially similar experiments were repeated on brain slices, which were then studied under the electron microscope. Even under extreme conditions of fluid surcharge, no extracellular space could be demonstrated, and the only cell element that was considerably involved in the swollen slices was astroglia.

TECHNICS

The central nervous systems of control animals and of those treated in vivo or the slices incubated in vitro were fixed for electron microscope study. The osmium tetroxide-potassium-dichromate fixative described by Dalton[13] and an isosmotic osmium fixative containing polyvinylpirrolidone and ions[14] were used. Fixation lasted for two hours at 4° C. Embedding was done in a mixture of butyl and methylmethacrylate (9:1) with prepolymerization and vacuum treatment. Thin sections were made with a Porter-Blum microtome and mounted on formvar films. An RCA EMU-2E electron microscope with compensated objective lens and with a 250 μ. condenser aperture and a 50 μ. objective aperture were used. The residual astigmatism was compensated with a Canalco stigmator.

RESULTS

Experiments leading to a general increase of the extracellular space. Adult white rats weighing 150 to 200 gm. were divided into 4 groups (Table 1). Group I consisted of nephrectomized rats that received, by injection eight and twenty hours after the operation, 2 intraperitoneal doses of saline or an isotonic solution without glucose for intraperitoneal dialysis[15] equivalent to 20 and 30% of body weight. The rats were sacrificed six hours after the second injection, and the increase in body weight and the wet and dry weight of the brain and the liver were recorded. These results were compared with a group of untreated control rats (group II, Table 1).

TABLE 1

RESULTS OF EXPERIMENTS LEADING TO GENERAL INCREASE OF EXTRACELLULAR SPACE*

	Number of animals	Initial body weight	Final body weight	Percentage of body weight gain	Wet weight of brain (mg.)	Dry weight of brain (mg.)	Percentage of dry weight of brain	Wet weight of brain in mg. per 100 gm. of body weight	Dry weight of brain in mg. per 100 gm. of body weight	Water content of brain in mg. per 100 gm. of body weight	
Group I (Nephrex plus isotonic)	8	198	264	37.8%	1188 ± 95	245 ± 25	**20.6%**	594 ± 62	123 ± 11	475 ± 53	P > 0.1
Group II (Controls)	8	159	—	—	1070 ± 103	222 ± 19	**20.7%**	658 ± 55	142 ± 17	516 ± 53	
Group III (Cranex plus Nephrex plus isotonic)	8	170 (152)†	210	28%	1084 ± 58	200 ± 17	**18.8%**	616 ± 51	114 ± 10	502 ± 41	P > 0.1
Group IV (Cranex controls)	8	162 (142)†	—	—	1100 ± 45	214 ± 13	**19.4%**	674 ± 43	131 ± 9	543 ± 40	

*Values expressed are mean values ± standard deviation (see explanation in text). †Body weight forty-eight hours after craniectomy

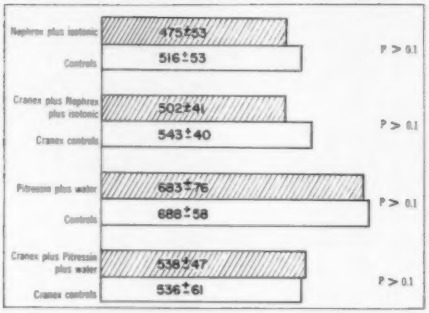


Fig. 1. Water content in milligrams per 100 grams of body weight of the brain in the different groups of experimental and control animals. The shaded portions correspond to experimental animals and the open portions to controls. Differences between all paired groups of animals are not significant.

Group III consisted of rats submitted to an extensive biparietal craniectomy in order to permit the expansion of the brain. After twenty-four to forty-eight hours, these animals were treated as group I. Group IV was a control of group III, consisting of craniectomized rats with no other treatment and maintained with water ad libitum.

The water content of the brain was expressed in milligram per 100 gm. of body weight, and the differences between the groups were calculated by the t test of Fischer (Table 1). Calculations were also made on the basis of brain weight in milligrams per 100 sq. cm. of body surface; the results were similar. The results expressed in percentage of dry weight, with the method suggested by Elliot and Jasper,[16] were also similar (Table 1).

The results obtained in these 4 groups of rats are summarized in Table 1 and typical figures are expressed diagrammatically in Figure 1.

It can be observed that, under these drastic experimental conditions in which there is a general increase of about 30 to 40% of body weight, the water content of the brain does not change. This is even more striking when compared with the changes occurring in the water content of an organ that has an extracellular space such as the liver (Table 2).

In groups I and III, histologic examination revealed a gelatinous edema of the hypodermis and an interstitial fluid infiltration of muscle, liver, and testis. Examination of the brain tissue under the electron microscope revealed no alterations of normal structure.

Water intoxication. The classical experiments of Rowntree[17] on water intoxication were repeated in group V. An injection of 2.5 to 5 I.U. of Pitressin was given, and 50 cc. per kilogram of body weight of distilled water was administered by a gastric tube or by intraperitoneal injection after thirty minutes. After two to three hours, the typical convulsions with opisthotonos were observed. As controls, a group of intact animals (group VI) were sacrificed.

Group VII received the same treatment as group V, forty-eight hours after craniectomy; in group VIII, only craniectomized rats were used as controls.

As can be observed in Table 3, differences in the brain water content of these groups are not significant. With the electron microscope, no changes of the normal structure of the glia cells were observed in group V, and no extracellular space was visible.

Localized traumatic edema. Rats and rabbits under ether anesthesia were submitted to a stab wound in the parietal zone of the brain cortex. The animals were sacrificed at different intervals and the zone near the wound was fixed and studied under the electron microscope. A complete study of the reactional process at the site of the wound and in neighboring regions will be published elsewhere. Here, only some observations related to the early stages will be mentioned. In these, according to neuropathologic studies, a so-called reactional traumatic edema takes place. The localized edematous change is not due to the formation of a real extracellular space. The swelling seems to be essentially cellular and is located mainly in the cytoplasm of the astro-

TABLE 2
WET WEIGHT OF LIVER IN GROUPS I AND II

	Controls	*Nephrex plus isotonic*	P
Brain—mg. per 100 gm. of body weight	656 ± 65	594 ± 62	>0.1
Liver—mg. per 100 gm. of body weight	3856 ± 205	4689 ± 604	0.02

cytes. Comparison of Figure 3, which shows an astrocyte near the stab wound, with Figure 2, which corresponds to a normal control, shows the main difference to consist of swelling of the cytoplasm with a decrease in electron density. This change lends a real watery aspect to the astrocyte. The swelling comprises not only the cell body but also the long processes of the astrocytes. The vesicles of the endoplasmic reticulum are swollen or disappear and the mitochondria show varying degrees of alteration. In spite of these considerable changes of the astrocytes, the other cellular elements show few modifications. Only at the site of the wound, where necrosis occurs, are spaces occupied by blood and cell debris.

Incubation of brain slices. Allen[11] and Pappius and Elliot[12] have shown that slices of brain tissue incubated in isotonic solutions for thirty or more minutes swell considerably, with an increase in the water content. These results were interpreted as due to an increase of the so-called "extracellular" compartment of the brain. The authors used this technic to measure this space.

Our first experiments in general followed the methods proposed by Allen.[11] Brain slices of adult rats, 3 to 6 mm. thick, were weighed and immediately incubated under constant flow of oxygen in chambers maintained at 37° ± 0.2° C. or aerobically in a Warburg apparatus. As incubating media the following solutions were used:

Isotonic	
Ringer tyrode	908.25 cc.
Glucose, 0.3M	66.75 cc.
l-glutamate, 0.2M	25 cc.
Hypotonic	
Ringer tyrode	454.1 cc.
Distilled water	454.1 cc.
l-glutamate, 0.2M	25 cc.
Glucose, 0.3M	66.75 cc.
Hypertonic	
Ringer tyrode (double concentration)	908.25 cc.
Glucose, 0.3M	66.75 cc.
l-glutamate, 0.2M	25 cc.

The solutions were brought to a *p*H of 7.4 and adjusted with sodium chloride or distilled water to the following cryoscopic points: isotonic, $\Delta = -0.62°$ C.; hypotonic, $\Delta = -0.30°$ C.; hypertonic, $\Delta = -0.87°$ C.

After thirty minutes' incubation, during which the slices were constantly oscillating

TABLE 3

RESULTS OF EXPERIMENTS ON WATER INTOXICATION*

	Number of animals	Initial body weight	Final body weight	Percentage of body weight gain	Wet weight of brain (mg.)	Dry weight of brain (mg.)	Percentage of dry weight of brain	Wet weight of brain in mg. per 100 gm. of body weight	Dry weight of brain in mg. per 100 gm. of body weight	Water content of brain in mg. per 100 gm. of body weight	
Group V (Pitressin plus water)	8	145	192	26%	1202 ± 134	230 ± 50	19.1%	830 ± 10	159 ± 31	683 ± 76	P > 0.1
Group VI (Controls)	8	130.5	—	—	1139 ± 50	221 ± 31	19.5%	857 ± 30	170 ± 23	688 ± 58	
Group VII (Cranex plus Pitressin plus water)	12	175 (162)†	209	29%	1172 ± 61	238 ± 25	20.1%	673 ± 45	134 ± 42	538 ± 47	P > 0.1
Group VIII (Cranex controls)	12	176 (160)†	—	—	1187 ± 139	245 ± 41	20.7%	674 ± 62	140 ± 21	536 ± 61	

*Values expressed are mean values ± standard deviation (see explanation in text). †Body weight forty-eight hours after craniectomy

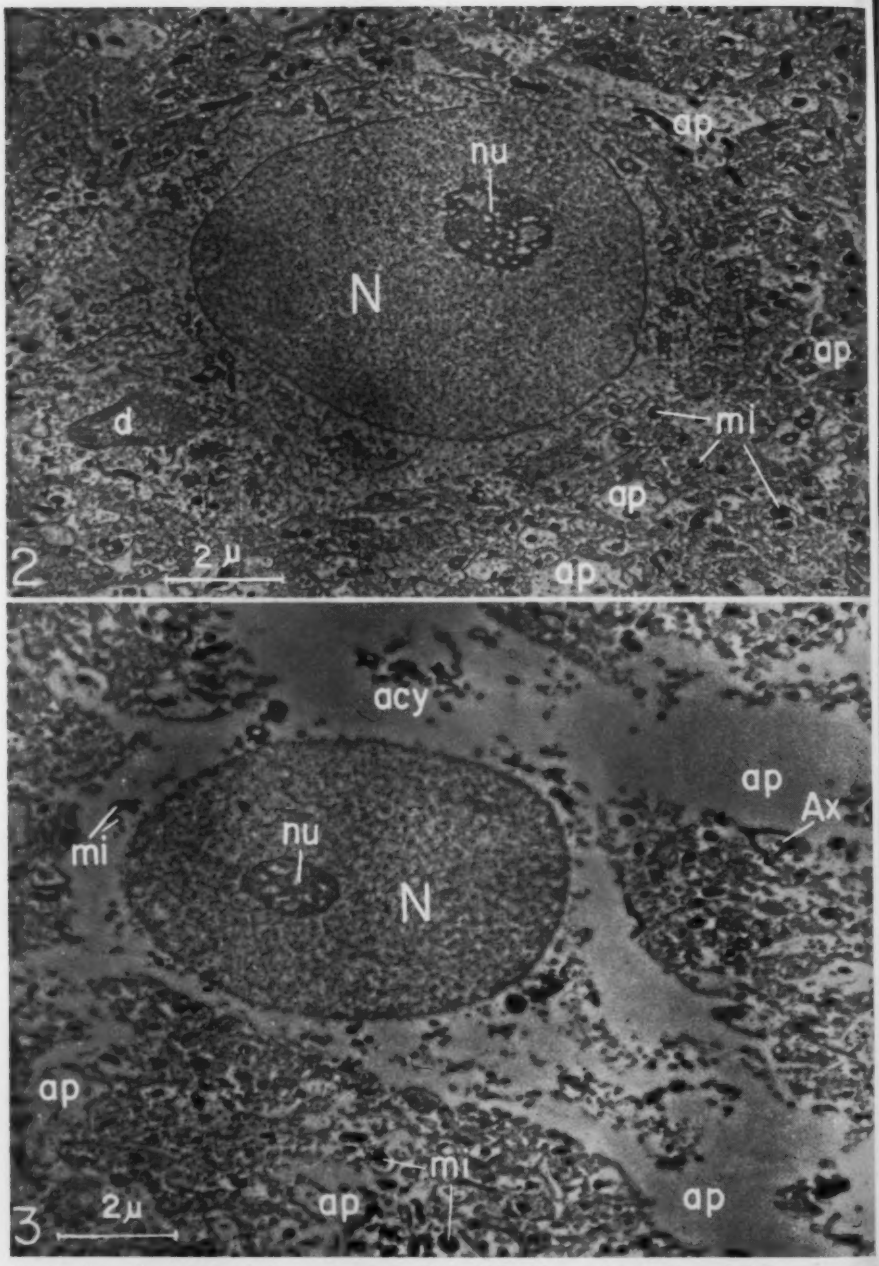


Fig. 2. Normal astrocyte of the brain cortex of a rabbit. N = nucleus; nu = nucleolus; ap = astrocytic processes; mi = mitochondria; d = dendrites. (× 9,400)

Fig. 3. Astrocyte of the zone of "traumatic edema" near a stab wound of the brain cortex of a rabbit. Notice the swollen astrocytic cytoplasm (*acy*) and processes (*ap*) and their watery aspect. Cytoplasmic organelles are altered. No extracellular space is seen in the surrounding neurophile. (× 9,400)

under oxygen flow, they were dried with filter paper and weighed again. The differences in weight were expressed in percentage of the initial weight. Control slices were immersed in isotonic solution and then dried and weighed in order to determine the increase in weight due to the adhesion of water. Both the material incubated in the chambers and that treated in the Warburg apparatus were fixed and studied under the electron microscope.

A second group of experiments was carried out according to some of the technics proposed by Pappius and Elliot.[12] Slices including only the brain cortex were used. The thickness was slightly larger than that recommended by the authors (1 mm.) in order to lessen the risk of mechanical damage of the brain structure. The slices were incubated for one hour at 38° ± 0 2° C. in a solution of Ringer phosphate without glutamate.[12] The slices were weighed in a torsion balance before and after treatment and treated as described above.

The main results of these in vitro experiments are presented in Figure 4.

The slices incubated in Allen's isotonic solution increased their weight by 11.7%. These results are coincident with those of Allen who, by deducing the "swelling factor," calculated an extracellular space of 17% with ferrocyanide and one of 14.5% with inulin.[11]

The electron microscope observations revealed a marked swelling of the cell body and processes of the astrocytes with decrease of electron density of the cytoplasmic matrix (compare Figs. 5 and 6). Mitochondria also showed considerable changes with fragmentation and vesiculation of the crests and diminution in electron density (Fig. 8). The cell body and dendrites of neurons showed, to some extent, a normal structure without swelling. On the contrary, the edges may appear compressed by adjacent swollen glial processes (Fig. 11).

With incubation in hypotonic solution after thirty minutes weight increased 25.9%. Electronmicrographs showed even more conspicuous changes. While the perikaryon and dendrites of neurons showed an increased electron density, probably due to retraction or compression, the astrocytic cytoplasm and all astrocytic processes showed considerable swelling with watery aspect of the matrix and mitochondrial alterations (Fig. 9). The synaptic endings also showed some swelling. In this case, as in all other in vitro incubations, *there was no apparent extracellular space* and all cell membranes were well preserved and in contact (compare Figs. 5 and 7 with Figs. 8 and 9).

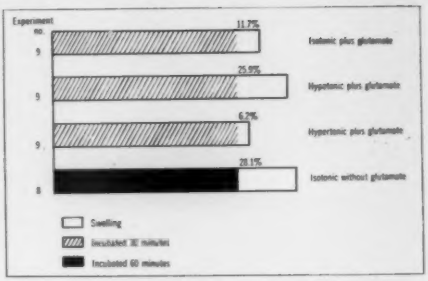


Fig. 4. Swelling of the brain slices incubated in different solutions, expressed in percentage of the wet weight gain

The slices incubated in hypertonic solutions increased their weight by 6.2% and, under the electron microscope, showed a discrete swelling of the astrocytes.

Slices treated for one hour according to the technic of Pappius and Elliot increased 28.1% in weight. The electron microscope observations showed no extracellular space but an enormous swelling of the astrocytes (Figs. 10, 11, and 12). With this treatment, mitochondria and synaptic endings were better preserved. Neurons showed normal structure, but the edges were sometimes compressed by the swollen glial processes (Fig. 11).

DISCUSSION

The nonexistence of an extracellular space and of "ground substance" in the central nervous system. The water and ion metabolism of the brain has been extensively studied by physiologic methods.[10] By using radioactive sodium and chloride, an extracellular space of the order of 32 to 34 and 31 to 33% was calculated.[10,18] These results were considered too large because it was thought that these electrolytes could in part be intracellular. Thus Allen[11] calculated, in vitro, an inulin space of 14.5% and a ferrocyanide space of 19%. Pappius and Elliot[12] concluded that the swelling

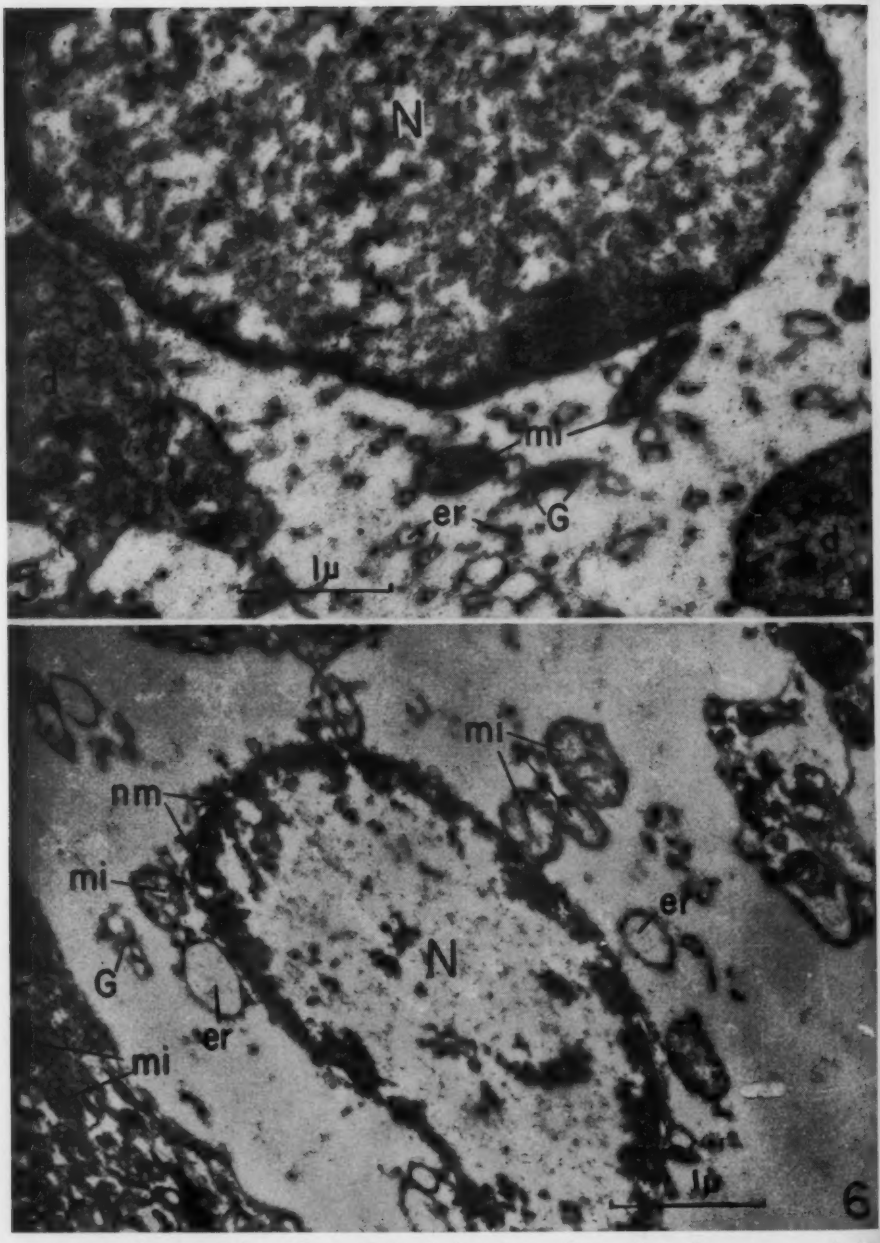
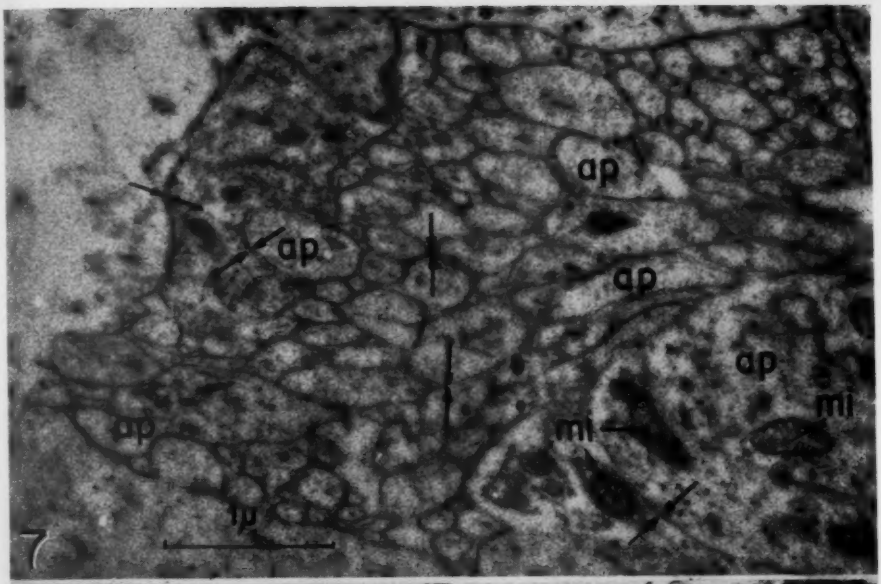


Fig. 5. Normal astrocyte of a rat brain. Notice the low electron density of cytoplasm as compared with that of dendrites (*d*). Golgi substance (*G*), dense mitochondria (*mi*), and vesicular endoplasmic reticulum (*er*) may be observed. (× 25,000)

Fig. 6. Aspect of a swollen astrocyte of an incubated nervous slice in isotonic fluid according to Allen. The cytoplasm is notably more watery, the ergastoplasm (*er*) is swollen, and mitochondria (*mi*) show alterations. The nuclear envelope (*nm*) is also swollen. (× 26,000)



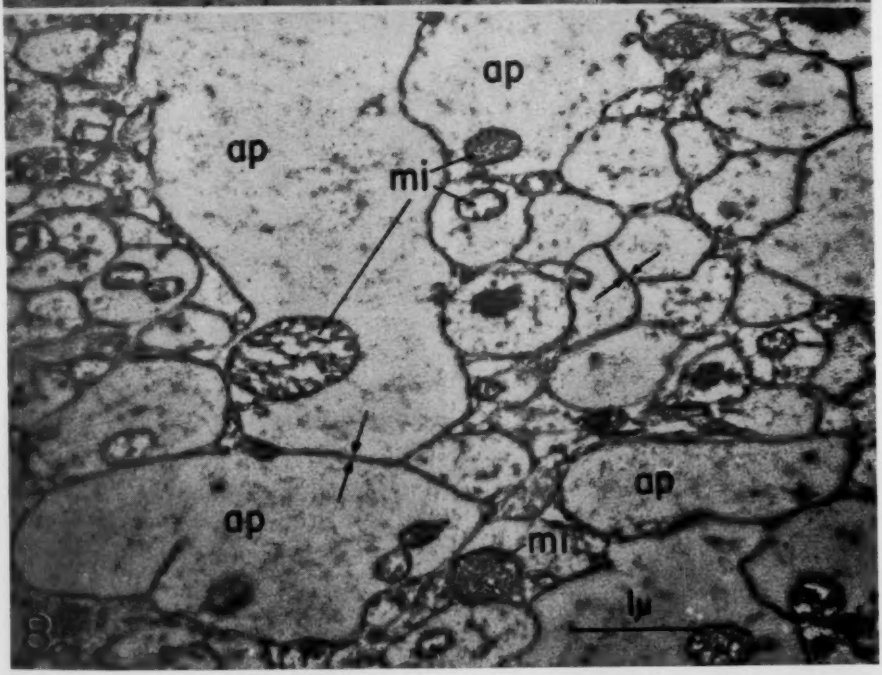


Fig. 7. Normal aspect of astroglial process (*ap*) sectioned in the vicinity of a capillary vessel. The arrows indicate the intimate apposition of the plasma membrane (× 26,500)

Fig. 8. Aspect of a zone similar to that of Figure 7. Astrocytic processes (*ap*) of nervous tissue slice incubated in isotonic fluid for thirty minutes are greatly swollen, but no separation between the apposed cellular membranes can be observed (see arrows). Swollen mitochondria (*mi*) can also be observed. (× 20,500)

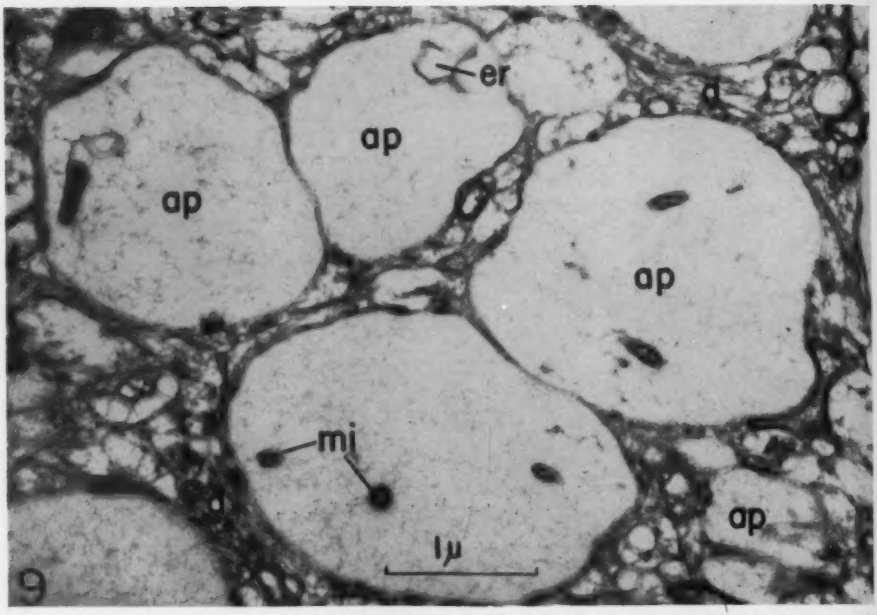


Fig. 9. Astroglial processes (*ap*) of nervous tissue incubated for thirty minutes in a hypotonic solution. The swelling and the alterations of mitochondria (*mi*) are more intense than in the isotonic solution (Fig. 8). The dendrites (*d*) are not swollen. (× 20,000)

water in the in vitro experiments with thiocyanate and sucrose in an aerobic medium without glutamate is extracellular.

The problem of extracellular space is intimately related to that of swelling and edema of the central nervous system. By in vivo experiments, Elliot and Jasper[16] differentiate 2 types of brain swelling: [1] a rapid one (the so-called "inflation"), probably due to vasodilatation and changes in the cerebrospinal fluid, and [2] a slower type (to which belongs the traumatic edema) which, according to the authors, is similar to the in vitro swelling of brain slices.[12]

All these and other physiologic experiments should be reinterpreted on the basis of the new knowledge of the structure of the central nervous system by electron microscopy, which demonstrates that, under normal conditions, there are no real extracellular spaces and that the plasma membranes of all cellular elements are in intimate contact with themselves and with basal membranes of the capillaries.[4,9,19]

Experimental results presented here show that it is practically impossible to produce a fluid surcharge of the brain in vivo. Such a drastic procedure as forced administration of saline solutions after nephrectomy (including in some cases an extensive craniectomy) did not lead to an increase of the water content of the brain. With this treatment, the general extracellular space of the body increased up to 30 to 40%. Also, the experiments of water intoxication resulted in no change of the water content of the brain and there was no extracellular space recognizable with the electron microscope. On this score, our results do not support the interpretation of Rowntree[17] that the convulsions produced by the treatment are due to cerebral edema. The observations on traumatic edema around a stab wound show that this is due to cellular swelling of the astroglia and not to the development of an extracellular space.

Crucial experiments to test the problem of the extracellular space are those performed in

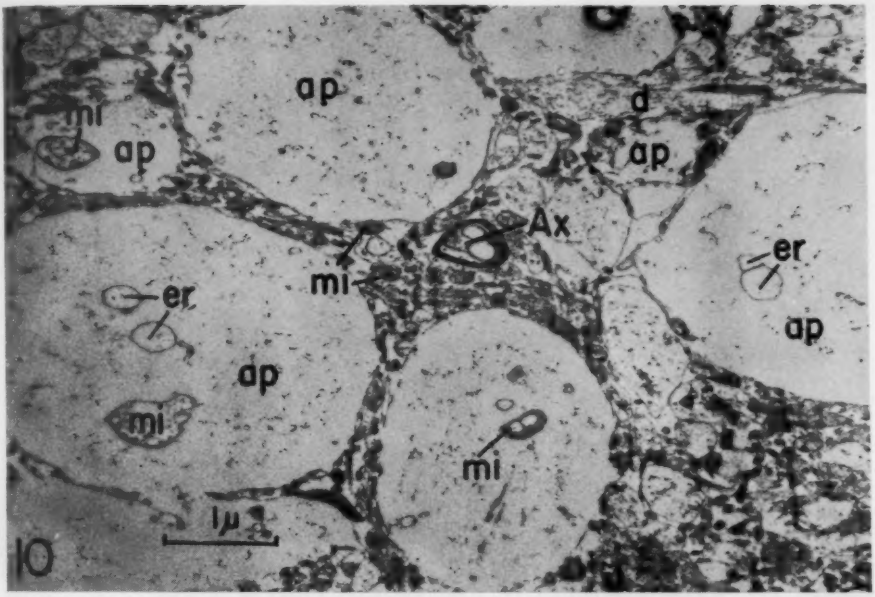


Fig. 10. Nervous tissue incubated for sixty minutes according to Pappius and Elliot. All astroglial processes (*ap*) are notably swollen and the dendrites (*d*) are well preserved. There is no extracellular space. Ax = axon; er = endoplasmic reticulum. (× 14,000)

vitro in which a definite fluid surcharge of nervous tissue occurs. This was as large as 25.9% in brain slices incubated in hypotonic solutions according to the technics of Allen[11] and 28.1% in those incubated isotonically in the solution of Pappius and Elliot.[12] However, even in extreme cases, there is no real extracellular space in the central nervous system.

Intimately related to the problem of the extracellular space is that of the existence of the so-called fundamental substance of the brain postulated by Hess.[20,21,22] With the use of histochemical technics for mucopolysaccharides, a PAS-positive substance was detected and localized in the intercellular spaces. This substance, with its special hydrophilic properties, has been related to water metabolism of the brain. Leaving out of discussion the purely cytochemical aspects of this problem, it can be said for certain that the technics used by Hess do not permit the exact localization of such a substance. The electron microscope shows that there is no extracellular space which could be occupied by the so-called "ground substance;" hence, if it really exists, it must be located within some of the cellular elements of the central nervous system.

Astroglia and the water and ion metabolism of the brain. Our electron microscope observations on the in vitro experiments show the strikingly different behavior of the various cell types found in the central nervous system in relation to the surcharge of fluid. While the neuronal elements (probably with the exception of the synaptic endings), the oligodendroglia, and the endothelial cells do not show marked changes, the astrocytes are considerably swollen and have a more watery aspect than in normal tissue. All the results reported here tend to exclude the existence of an extracellular space. They support the concept that astroglia constitutes a water-ion compartment interposed between the blood capillaries and the cerebrospinal fluid on one side and the cellular compartment proper represented by the neurons and all nerve expansions and pos-

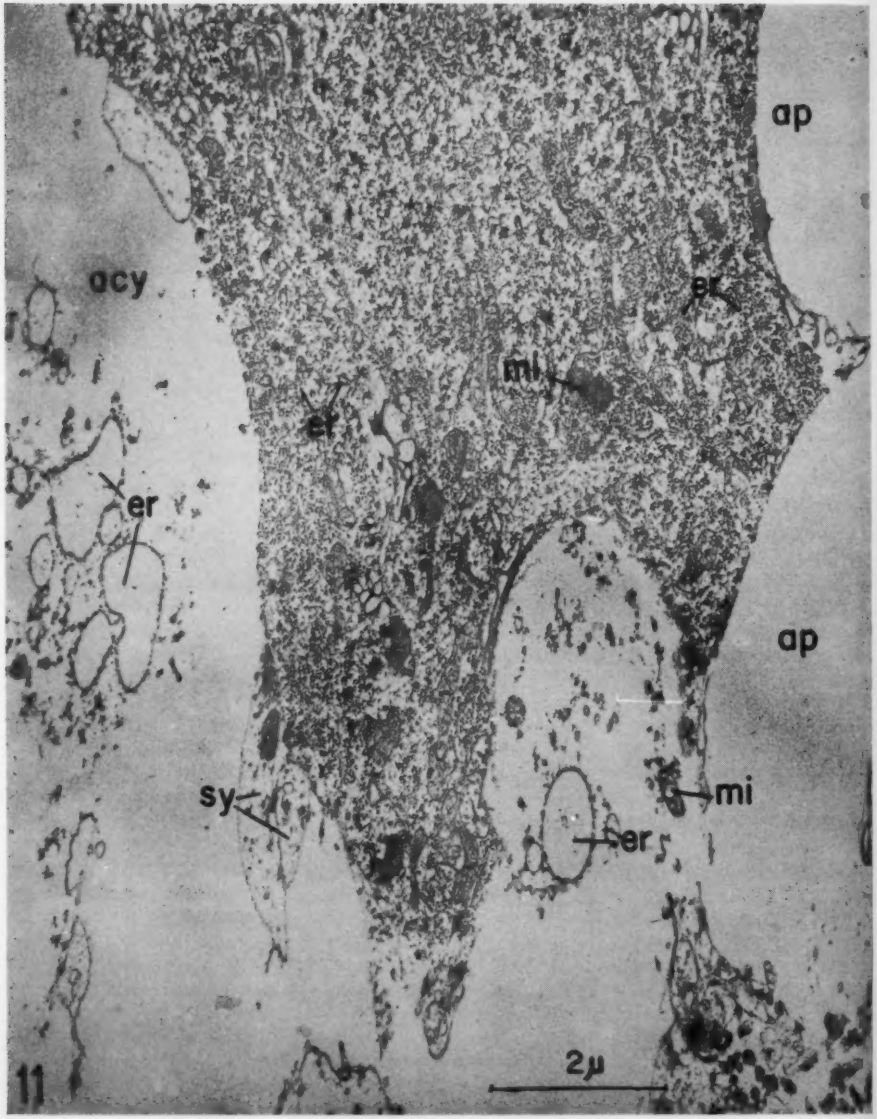


Fig. 11. Neuron and surrounding astrocytic cytoplasm (*acy*) and processes (*ap*) of the nervous tissue incubated in isotonic medium without glutamate for sixty minutes. The astroglia is greatly swollen while the neuron is well preserved. There is no extracellular space. Notice the preservation of the Nissl substance (*er*) of the neuron and the synaptic endings (*sy*). (× 11,000)

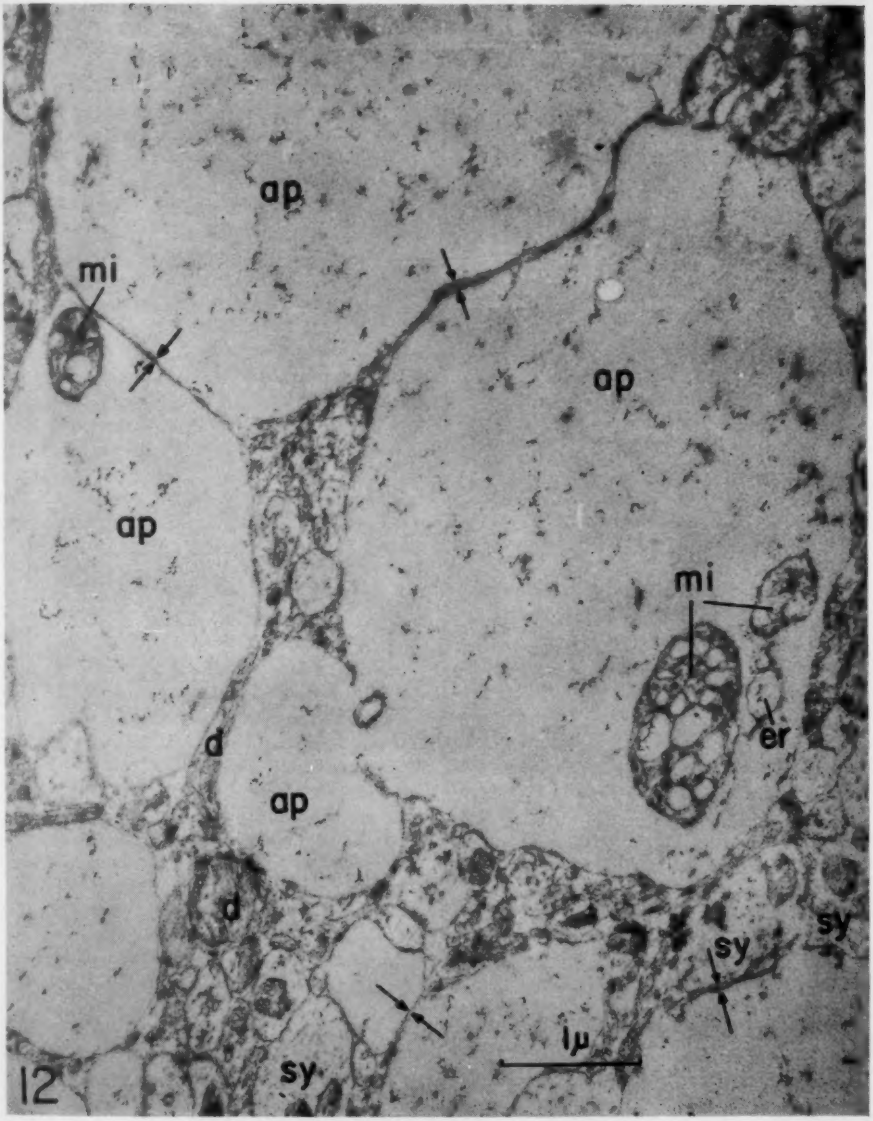


Fig. 12. Another aspect of the nervous tissue incubated in the same conditions as in Figure 11. The astroglial processes (*ap*) are swollen with alteration of mitochondria (*mi*). There is no formation of an extracellular space (see arrows). (× 14,000)

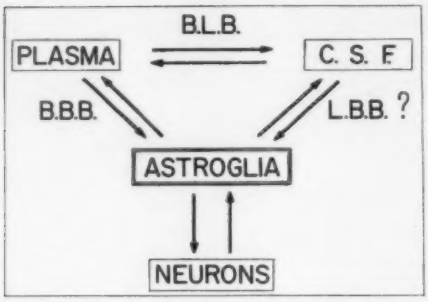


Fig. 13. Diagrammatic representation of the hypothetic relationships between plasma and cerebrospinal fluid with the neuron through the astroglia. LBB = liquor-brain barrier. BLB = blood-liquor barrier. BBB = blood-brain barrier (see explanation in text).

sibly oligodendroglia (Fig. 13). This water-ion compartment would be involved in the selection and transport of metabolites and fluid exchanges between the blood and the cerebrospinal fluid and the cellular compartment.

Electron microscope observations have demonstrated that the blood capillaries of the brain are intimately surrounded by the vascular feet of the astrocytes.[4,9,19] The plasma membrane of the glia cells is directly applied on the basal membrane of the capillary with no interposed extravascular space. This structural relationship may explain the special permeability properties shown by brain capillaries which are known as the blood-brain barrier (BBB). In his recent analysis on glial function, Lumsden[23] postulates that the BBB is probably represented by the entire gelified matrix of the glial cytoplasm. The properties of this BBB are to some extent similar to those of an active transport across a cell membrane[24] and probably related to the need for a more selective interchange between the blood and nerve cells. These facts, combined with the structural relationships revealed by electron microscopy, lead us to think that the BBB is morphologically represented by the plasma membrane of the vascular feet of the astrocyte. The special permeability properties of this membrane and the lack of an extracellular space may be involved in the homeostatic mechanism that prevents, in vivo, the fluid surcharge of the brain. In the brain slices, the BBB does not operate and astrocytes, either intact or with their processes sectioned, are directly exposed to the incubating medium. Here, either in hypotonic or isotonic solutions, intake of fluid by astroglia is considerable and, surprisingly, even in hypertonic solutions the astrocytes are swollen slightly.

This fact may be related to recent studies that demonstrate the hypertonicity of the cerebrospinal fluid.[25] Because of the intimate relationships of this fluid compartment with the nervous tissue and the high rate of ionic exchange existing between them,[26] Davson postulated that a hypertonic extracellular cerebral fluid should be secreted by the brain capillaries.[27] The experimental results reported here do not support this hypothesis. On the contrary, they suggest that this hypertonic water-ion compartment may be represented by the astrocytes—cells that are related not only with the blood capillaries but also with the pial surface of the brain. At this level, the relationships between the glia and the cerebrospinal fluid are not well known and more study is needed to establish whether there is also a barrier of selective permeability in this site.[28,29]

Some of the results and problems discussed here on the relationship between fluid compartments in the brain are represented diagrammatically in Figure 13. Astroglia, in spite of being a cellular element, has some of the characteristics and functions of the extracellular space of other tissues. It constitutes a central water-ion pool interposed between the blood and the cerebrospinal fluid and the cellular compartment proper represented by the neurons. This pool would be involved in the transport of metabolites selected at the level of the BBB and could act as a fluid cushion for the mechanical support of the neurons. Furthermore, it could act as an environment for the maintenance and replacement of gradients of K^+ and Na^+ at the bioelectrically active surface membrane of the neurons.

This proposed diagram discards entirely the existence of an extracellular space and attributes to astroglia a central role in the water-ion metabolism of the central nervous system. However, several of the side pathways are little known and should be investigated further.

SUMMARY

In the present work, no change in the water content of the rat brain was found in a series of experiments leading to the increase of the general extracellular space such as bilateral nephrectomy followed by injection of large doses of isotonic solution or a similar treatment after craniectomy. Hydric intoxication with water and Pitressin in normal and craniectomized rats also did not change the water content of the brain. In all these cases, electron microscope study showed no alteration in the structure of the central nervous system.

Electron microscope study of the zone of "traumatic edema" in stab wounds of the brain of rats and rabbits showed that this type of lesion is not a true edema and that swelling is mainly located in the astrocytes.

Considerable increase in water content of brain slices was obtained after incubation in an isotonic solution for thirty to sixty minutes. The electron microscope study showed that the swelling is not due to the increase or to the formation of an extracellular space but to a considerable swelling of astroglia. Incubation in a hypotonic solution produced more marked swelling, and even a hypertonic solution might cause mild swelling of astrocytes. In all cases, neurons were not swollen and even showed compression of the perikaryon and dendrites by the swollen astrocytes.

On the basis of these morphologic and experimental evidences, it is concluded that there is no extracellular space or intercellular ground substance in the central nervous system. The conclusion is also reached that astroglia functions as a water-ion compartment in the central nervous system, which is involved in the selective transports of fluids and metabolites between the vascular system and the neurons.

ACKNOWLEDGMENT

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Normal air encephalogram in patients with tumor of the brain

Report of 8 cases

Ronald W. Angel, M.D., and D. Frank Benson, M.D.

A MAJOR PROBLEM in clinical neurology is the management of patients with suspected brain tumor. Pneumoencephalography has been accepted as a valuable technic in the investigation of these patients. While abnormal air studies may provide a basis for diagnosis and therapy, normal studies are of more limited value. That normal air shadows do not exclude an expanding intracranial lesion is well known.[1–9] However, few authors have emphasized the fact that a long latent period may occur between the time of normal air encephalography and the ultimate demonstration of a brain tumor. The present report concerns 8 patients in whom brain tumor was diagnosed more than two years after normal air studies.

In 1937, Savitsky and Bender[1] reported 9 patients with brain tumor and normal air encephalograms. The latent period between air studies and surgical diagnosis varied from a few weeks to three and a half years. In 1938, Pennybacker and Meadows[2] reported 4 patients with normal ventriculograms in the presence of cerebral tumor and a latent period ranging from five days to thirty months. In 8 of the 10 cases reported by Poppen and Peacher,[3] the interval varied from two days to two months. The longest interval reported in their series was two years. Merritt and Brenner[4] described 3 patients who had normal pneumoencephalograms at intervals of seventeen months, four years, and six years before discovery of brain tumor. Martin, Webster, and Gurdjian[5] cited 5 patients with negative air studies followed by a tumor diagnosis within seventeen weeks to five and one-fourth years.

Cases in the present series were selected from a total of over 140 primary brain tumors diagnosed and treated at the Veterans Administration Hospital, San Francisco, from 1946 to 1958. Criteria for inclusion in this study were:

1] Initial workup for suspected brain tumor.

2] Normal pneumoencephalograms considered to be of diagnostic quality.

3] A latent period of two years between the first air studies and surgical diagnosis of a brain tumor.

CASE REPORTS

Case 1. A 34-year-old man was admitted to the hospital on July 3, 1953, after his first convulsion. The seizure had begun with a short period of disturbed mental function after which he fell to the right and had a generalized convulsion. Neurologic examination showed a mild right hyperreflexia, equivocal extensor toe signs on the right, and evidence of an old left ulnar nerve injury. Spinal fluid and other laboratory studies were normal. The electroencephalogram showed a left temporal focus. Pneumoencephalograms done July 31 were read as normal. He was discharged on anticonvulsants.

A year later, he began to have seizures consisting of intermittent periods of aphasia. He was readmitted July 1, 1955, and examination showed mixed aphasia, dyscalculia, dyspraxia, and impaired concentration. The optic disks were blurred, and a partial right homonymous hemianopsia was found. Ventriculograms done on July 7, 1955, showed evidence of a left parietal expanding lesion. Surgical biopsy revealed glioblastoma multiforme.

Case 2. A 35-year-old man was transferred to the San Francisco VA Hospital on April 26, 1951, for irradiation of a left frontal astroblastoma. His illness had begun in 1947 with a generalized

From the Veterans Administration Hospital, San Francisco.

tonic-clonic convulsion. He was studied at another hospital where pneumoencephalograms were considered normal. In 1948, he began having seizures characterized by shaking of the right hand, staring, and involuntary repetition of words. In early 1951, his condition deteriorated acutely and, on his second hospitalization in March 1951, he was comatose with intermittent twitching of the right upper extremity. Neurologic examination revealed a right spastic hemiparesis. Ventriculography showed a left frontal mass. Through a frontal bur hole, a ventricular needle was inserted into a cyst which contained 80 cc. of fluid with a high protein content. On April 14, 1951, a left frontal craniotomy was performed and no tumor or cyst was visualized. However, a biopsy taken at the time was interpreted as astroblastoma.

Case 3. A 54-year-old man was admitted to the hospital on October 7, 1957. His illness began in June 1951 with a grand mal seizure. He was studied at another hospital where ventriculography was performed, revealing no evidence of a surgical lesion. He was placed on anticonvulsants and had infrequent seizures thereafter. In 1954, he had a series of left-sided jacksonian convulsions with postictal paralysis of the left hand. After this, seizures continued in spite of anticonvulsant drugs. In 1956, he was treated at a state hospital because of paranoid delusions. During the course of electric shock therapy, he developed paresis of the left upper and lower extremities. This motor deficit progressed slowly to become a left spastic hemiparesis. In September 1957, x-rays showed a shift of the pineal to the left. On admission, he showed a spastic hemiparesis with plantar extensor responses and astereognosis on the left side. X-rays revealed calcification in the left parietal region. Electroencephalogram revealed a slow wave focus in the right frontal and temporal areas. On October 14, 1957, a right carotid angiogram showed evidence of a parietal lesion. Craniotomy and surgical biopsy were done on October 22, 1957. The tumor was a glioblastoma multiforme.

Case 4. A 42-year-old man entered the hospital on October 7, 1958 with headaches of three months' duration. His present illness had begun in May 1948 with a series of 5 generalized tonic-clonic convulsions. In March 1949, he had been admitted to another hospital because of these seizures. At that time, the neurologic examination and laboratory studies, including spinal fluid and electroencephalogram, were all normal. A pneumoencephalogram showed slight dilation of the entire ventricular system without any focal deformity. He was discharged on Dilantin and phenobarbital. During the next eight years, he had 10 or 12 more seizures but these stopped in December 1957.

In July 1958, he began to have headaches and occasional blurring of vision. He was found to have papilledema, slight ataxia, and dyscalculia. Minimal weakness was found in the right upper limb, and the right ankle jerk was more active than the left. X-ray showed a left frontal intracranial calcification. Ventriculography on October 14, 1958 revealed evidence of a deep-lying tumor in the left frontoparietal region. At operation, an astrocytoma was found to extend from the left frontal region into the lateral ventricle and foramen of Monro.

Case 5. A 33-year-old man was admitted to the hospital on July 3, 1952 because of nocturnal convulsions which had begun eight months earlier. Following a series of 10 nocturnal convulsions in May 1951, he was administered phenobarbital. The seizures were stopped, but progressive personality changes were noted. On admission, the neurologic examination and laboratory studies were normal. Routine electroencephalogram was normal, but activation with Metrazol injection produced a right-sided slow wave focus and clinical seizure phenomena. Pneumoencephalograms done on July 10, 1952 were normal. The patient was discharged on anticonvulsant medication.

In July 1953, he was treated at another hospital for a series of left-sided seizures. In May 1958, he collapsed following a short period of occipital headaches, vomiting, and inability to use the left arm. On May 14, 1958 he was readmitted to the hospital in a coma and with left hemiplegia; fixed, dilated pupils; and papilledema. Ventriculography done the day of admission revealed a right frontal lobe mass which was found to be a glioblastoma multiforme.

Case 6. A 25-year-old man was admitted to the hospital on January 25, 1953 after having 3 seizures in the preceding six weeks. Of these seizures, 1 was a generalized convulsion, 1 was characterized by semiautomatic behavior, and 1 consisted of a short period of anomic aphasia. The general physical and neurologic examinations were negative. Laboratory studies, including numerous electroencephalograms were normal. A pneumoencephalogram done February 5, 1953 was interpreted as normal. An angiogram done February 12 was considered to be within normal limits. The patient was placed on Dilantin and was followed in the clinic for three and a half years. In this time, he had numerous minor seizures characterized by feeling a cold draft on his face, the sensation of someone standing behind him, and a short period of aphasia. He was readmitted on October 14, 1957 after a generalized convulsion. Neurologic examination disclosed only an early papilledema. A ventriculogram done on October 25, 1957 showed a filling defect in the left temporal lobe. Craniotomy revealed a fibrillary astrocytoma involving most of the left temporal lobe.

Case 7. A 41-year-old man was admitted to the hospital on February 27, 1958 for evaluation of progressive right hemiparesis. His illness had started in 1951 with a series of 6 seizures which began with movements in the right foot and became generalized. In July 1951, he was examined in an army hospital where studies—including a

pneumoencephalogram and bilateral carotid angiography—were normal. Anticonvulsant therapy was started, and the patient returned to military duty. In May 1956, he was hospitalized following another major seizure. Anticonvulsant medication was increased, and he had no further seizures. In March 1957, he noted the onset of right hemiparesis. In May 1957, a neurologic workup, including pneumoencephalogram, was normal. Because of progressive right-sided weakness, he was discharged from the service and entered the hospital in February 1958. Neurologic examination revealed a right spastic hemiparesis, right hemisensory deficit, and right homonymous hemianopsia. Carotid angiography on March 11, 1958 revealed a space-occupying lesion in the left posterior parietal region. At craniotomy, an astrocytoma was partially removed.

Case 8. A 25-year-old male was admitted to the hospital on March 5, 1948 for evaluation of right-sided focal motor seizures. He had been hospitalized elsewhere in February 1948 with a one-year history of major seizures. A pneumoencephalogram done on February 23, 1943, was normal. He was given Dilantin but continued to have seizures characterized by expressive aphasia and involuntary movements of the right limbs followed by unconsciousness. Examination on admission to the hospital revealed a minimal right hyperreflexia and questionable changes in cortical sensation on the right side. An electroencephalogram showed a left frontotemporal focus. Pneumoencephalography on March 8, 1948 showed evidence of a left frontoparietal mass. Craniotomy revealed a tumor which was called fibrillary astrocytoma. The patient was rehospitalized in July 1953 because of recurrent seizures and progressive right hemiparesis. A second craniotomy was performed, and, this time, the tumor was considered to be an oligodendroglioma.

DISCUSSION

These case histories bring out several points concerning the management of patients with suspected brain tumor. Foremost is the fact that a long interval may elapse between normal air studies and the ultimate diagnosis of a brain tumor. In our patients, the latent period ranged from two years to over nine years and averaged more than five years. Taken together with other series reported in the literature, these cases demonstrate clearly that, following normal air studies, there is no interval after which one can dismiss the possibility of an expanding intracranial lesion. Once the suspicion of brain tumor has been raised, the clinician should always bear this possibility in mind, regardless of normal air contrast studies and the passage of many months or years.

A second point illustrated by these case histories is the diagnostic value of localizing signs. In 7 of the 8 patients, at least one finding in the history, physical examination, or electroencephalographic studies pointed correctly to the diagnosis of a focal lesion. In Case 5, the routine diagnostic studies—including history, neurologic, and laboratory work—were all within normal limits. However, the activated electroencephalograms provided clear evidence of a focal lesion in the right hemisphere which later was confirmed at operation.

A third point illustrated by these cases is that a good response to anticonvulsant drugs should not lull the physician into dismissing the possibility of brain tumor. Case 7 illustrates this fact especially well. His first symptoms were generalized convulsive seizures beginning in the right foot. On anticonvulsant drugs, the seizure phenomena were confined to episodic weakness and involuntary motions of the right lower extremity. Not the seizures, but a progressive hemiparesis led to repeat diagnostic studies. Other patients in this series showed either complete or partial control of seizures after anticonvulsant drugs were started. Any epileptogenic focus, whether of traumatic, vascular, inflammatory, or neoplastic origin, may respond to anticonvulsants. A favorable response is, therefore, of limited value in differential diagnosis.

Since these brain tumors escaped detection by the usual diagnostic study, the question arises whether they were of some unusual type, either pathologically or in terms of location. The series contained 3 glioblastomas, 3 astrocytomas, 1 astroblastoma, and 1 oligodendroglioma. Certainly, the elusiveness of these tumors is difficult to explain on the basis of benign histologic features. Anatomically, the tumors involved the frontal, parietal, and temporal lobes. Thus, the absence of ventricular displacement does not appear to be related to any particular location of the tumor.

Of interest is the fact that 6 of the 8 tumors were located in the dominant left hemisphere. While this series is too small for statistical significance, possibly tumors of the major hemisphere produce earlier and more disabling symptoms than equivalent tumors of the minor hemisphere. This could lead to earlier diagnostic studies, perhaps at a time when the mass

is not large enough to be visualized by air-contrast studies.

SUMMARY AND CONCLUSIONS

A study was made of brain tumors in 8 patients with normal air encephalograms. The interval between initial studies and the demonstration of brain tumor ranged from two years to more than nine years. The presence of a brain tumor cannot be ruled out either by normal air studies, prolonged period of observation, or a satisfactory response to anticonvulsant medication.

The authors acknowledge with thanks the valuable assistance of Prof. Henry W. Newman in the preparation of this manuscript.

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Combined degeneration of globus pallidus and dentate nucleus and their projections

Meta A. Neumann, M.S.

DISEASES WITH CLINICAL symptomatology indicating basal ganglia lesions are notoriously protean in their pathologic involvement. Similarly, in cerebellar disorders, the clinical findings and the specific brain structures damaged in the disease process are not precisely correlated. Strictly speaking, the cerebellum, basal ganglia components, and thalamus are all parts or sublevels of the extrapyramidal system; progressive atrophy or degeneration, usually considered abiotrophy, is generally confined to one gross element of this complex system. The areas mentioned and other subcortical nuclei are intricately related, but opinion is not unanimous on the origin, course, and termination of some of these pathways.

In the voluminous literature on the anatomy and pathology of the basal ganglia and cerebellum, cases involving atrophy of the pallidal and dentate systems in the same brain are rarely mentioned. The 2 cases under study showed this combined degeneration; 1 patient clinically showed constant involuntary hyperactivity and the other showed progressive rigidity. Data are presented to demonstrate that intrasystem changes are the basis for the diametrically opposed syndromes displayed by the 2 patients.

CASE REPORTS

Case 1. A Negro woman in her early thirties was admitted to St. Elizabeths Hospital on December 2, 1942. She was unable to walk; her hands made constant flail-like choreiform, purposeless movements; her head moved ceaselessly from side to side.

The patient was able to grasp the examiner's hand only after numerous trials. She was said to have many grimacing mannerisms. Her pupils were round, equal, and reacted slowly to light and in convergence. Many involuntary movements of her eyeballs were noted. Her tongue showed a coarse tremor and deviated slightly to the left on protrusion. She maintained her legs in scissors-like position, with only occasional low-amplitude movements. She was unable to volitionally place either of her heels on the opposite knee. The deep tendon reflexes were symmetrically hyperactive. Abdominal reflexes were not elicited. Knee and ankle clonus were present. No Babinski signs were observed.

The patient's birth and early development were said to be normal. She had the usual childhood diseases and also had influenza during the epidemic of 1918 and pneumonia with high fever in 1932 or 1933. She attended school only a few years and apparently did poorly; she never learned to write. When she was 16 years old, she got a job as a nursemaid and worked in that capacity for many years.

About seven years before hospitalization, she ceased work because she did not seem to have enough energy to do anything. She first had difficulty walking, two years before admission. In the spring of 1942, she had to hold on to things to support herself. She managed to crawl around the house for a while, but soon her arms began to shake and she could not maintain her grasp. Her mother said the patient was quiet while asleep.

The patient had a grand mal convulsion three days after admission and had several more in succeeding months. These convulsions were only partially controlled by Luminal therapy. Rabellon was ineffective for control of her muscular activity. An electroencephalogram recorded after sedation with Sodium Pentothal was within the range of normal variation. During the following years, the patient's condition progressed. Her movements were said to be increased by attention. She seldom spoke spontaneously and never seemed psychotic. After November 1945, she spent most of her time in bed. By April 1947, her explosive speech was incomprehensible.

The patient died from a respiratory infection on June 30, 1948. Laboratory tests throughout her five and one-half years of hospitalization were within normal range.

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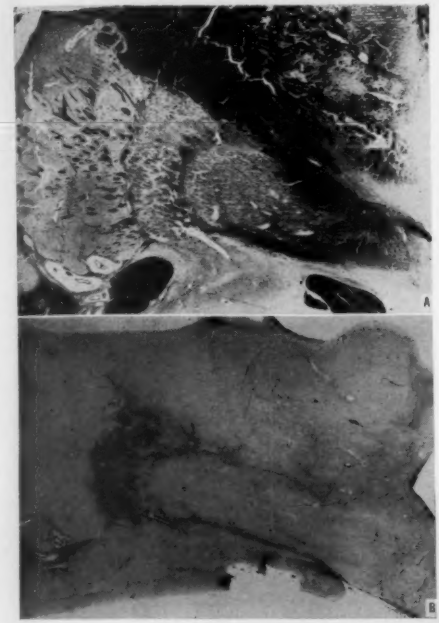

Fig. 1. *Case 1.* (A) Loss of myelin in globus pallidus, most extreme in external segment. Weil stain. (B) Severe reactive gliosis in external pallidal segment and in ansa and fasciculus lenticularis. Holzer stain

Necropsy:* Bacteriologic and histologic studies confirmed that Friedländer pneumonia was the cause of death. Other visceral findings, gross and microscopic, were not significant. The brain weighed only 860 gm., but the gyri had not shrunk, and the vessels were free from sclerotic change. On dissection, no focal lesions were observed. Since neurologic symptoms pointed to disease of the extrapyramidal system, numerous sections were taken for histologic examination.†

Microscopic examination. Brain: Sections from 3 cortical areas showed slight diffuse loss of nerve cells. Some of the remaining ones were pyknotic; others appeared as shadows. In one of the sections from the posterior part of the left frontal lobe, poorly demarcated loss of myelin occurred in the corona radiata and ventral part of the corpus callosum. Focal swellings and fragmentation of sheaths and beading of individual axis cylinders were observed in dystrophic areas. Holzer stain showed slight astrocytosis in these regions.

Approximately symmetric sections were studied from the basal ganglia. The most prominent feature was atrophy of each globus pallidus and its efferent tracts. Myelin loss occurred in the external and internal medullary lamina, especially in the external lamina (Fig. 1A). In the external division on both sides, practically no nerve cells remained; few nerve cells were found in the internal segment. Glia nuclei were increased in both divisions, but, with the Holzer technic, the fibrillary gliosis was much more intense in the external division (Fig. 1B). Reactive gliosis was seen in the regions of ansa and fasciculus lenticularis, anterior perforated substance, ventral half of the external capsule, and subcallosal fasciculus. The large myelinated bundles of the caudate nucleus and putamen were intact, but the fine sheaths were slightly decreased and poorly stained. No gliosis occurred in the striatum.

The striatal nerve cells had pale, swollen, or

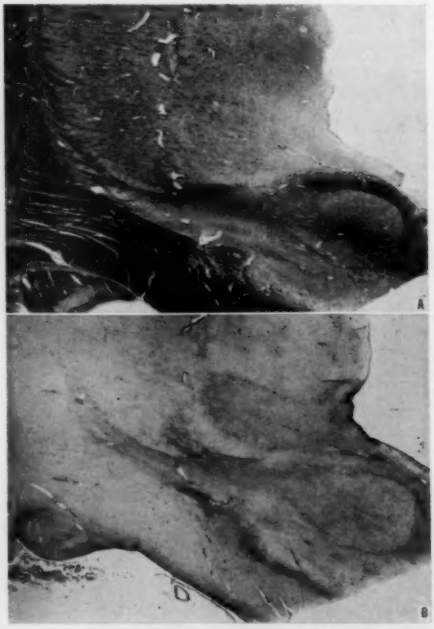

Fig. 2. *Case 1.* (A) Dystrophy of brachium conjunctivum and loss of myelin in medial and centromedian nuclei of left thalamus and of subthalamus. Weil stain. (B) Same area, showing gliosis in dystrophic regions and in the reticular zone of substantia nigra. Holzer stain

*Autopsy was performed thirteen hours after death by Dr. K. H. Langenstrass.

†Weil, Holzer, Davenport, Klüver-Barrera,[1] Marsland and Glees,[2] Perls, hematoxylin-eosin, toluidine blue, phosphotungstic acid hematoxylin, and oil red O pyridine stains were done.

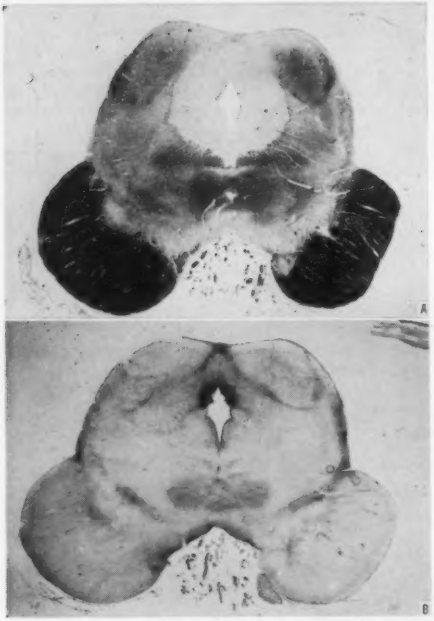

Fig. 3. *Case 1.* (A) Dystrophy of brachium conjunctivum. Weil stain. (B) Gliosis in decussation of brachium conjunctivum, and reticular zones of substantia nigra. Holzer stain

scarcely visible cell bodies; the nuclei were pale and vesicular. The large neurons were most severely involved. A few deposits of iron-reacting material were seen in each pallidum, free or in vessel walls. The grossly faint blue color of the normal pallidum (Perls' method) was not present. Lipoid deposits were demonstrated around some small vessels and were most numerous in the globus pallidus, but never extensive.

In the symmetric diencephalic sections, extreme dystrophy of the brachium conjunctivum was prominent bilaterally (Fig. 2A). Degenerated sheaths and loss of small nerve cells were apparent in the red nuclei. Myelin sheaths were decreased and remaining sheaths stained poorly in the medial and centromedian nuclei, the reticular zone of the substantia nigra, and the posterior part of each pallidum where nerve cells were absent. The medullated band separating the medial and lateral thalamic nuclei was almost nonexistent. These pale areas were in marked contrast to the deeply stained sheaths of normal regions (Weil stain).

In the thalamus, no apparent loss of neurons was seen but many neurons had poor staining reaction or degenerative changes. The substantia nigra was normally pigmented, but this region and the centromedian nuclei were peculiarly spongy. Holzer method demonstrated gliosis in the dystrophic areas (Fig. 2B): brachium conjunctivum, centromedian and red nuclei, stratum intermedius pedunculi, pallidum, and external capsule. The gliosis in the region between the nigra and peduncle probably involved fibers from the pallidum to lower levels.

The subthalamus was not well defined in the myelin preparations due to absence of the myelinated capsule which is composed chiefly of fibers from the pallidum. However, when interrupted serial sections from the slightly more rostral area were studied with Klüver-Barrera combined cell and myelin stains, the nucleus contained approximately its normal complement of nerve cells. The cells appeared somewhat shrunken and surrounded by clear spaces, thus resembling the spongy nigra and centromedian nuclei. This nucleus was reduced in size compared with a normal series.

The small midbrain showed decrease in size of the brachium conjunctivum (Fig. 3A). The remaining sheaths of the decussation were well stained, but, in the silver preparation, individual fibers were thickened and beaded. Dense fibril-

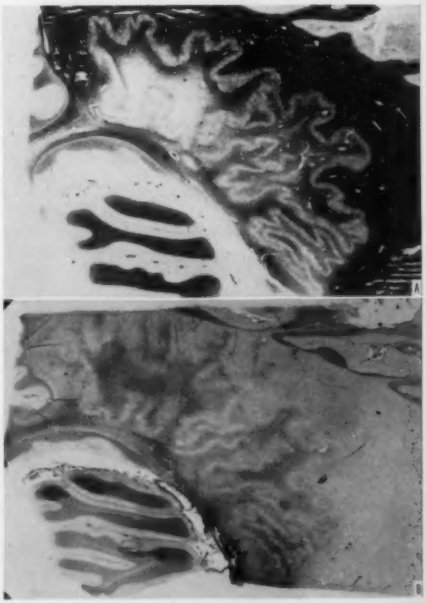

Fig. 4. *Case 1.* (A) Normal configuration of left dentate nucleus with focal loss of myelin in hilus. Weil stain. (B) Gliosis in hilus of left dentate nucleus. Holzer stain

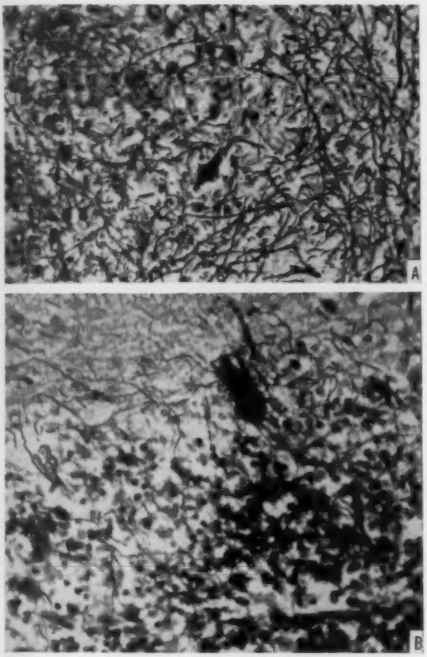

Fig. 5. *Case 1.* (A) Degenerated nerve endings and terminal buttons in dentate nucleus; note cluster of degenerated buttons around diseased nerve cell. (Glees stain, × 600). (B) Purkinje cell showing degenerative changes and loss of adjacent cells and empty baskets. (Glees stain, × 480)

lary gliosis was noted in the decussation of the atrophic brachium, midtectum, capsules of the inferior colliculi, dorsal periaqueductal region, dorsal and ventral areas of the locus niger, and lateral tegmentum (Fig. 3B). The spongy appearance of the nigra was also noted at this level. In the dorsal tegmentum, many nerve cells showed central chromatolysis and eccentric position of their nuclei.

In the upper pons, the pallor (Weil stain) and gliosis (Holzer stain) of the brachium conjunctivum were prominent (Fig. 8A). Glial hyperplasia was seen throughout the tegmentum. Each locus cæruleus had loss of pigmented nerve cells which was more noticeable on the side where myelin decrease and reactive gliosis were more intense.

Approximately symmetric sections from the cerebellar hemispheres showed large dentate nuclei with complex folds bilaterally. Each hilus had central areas of myelin loss in which fragmented sheaths with focal swellings were prominent (Fig. 4A). Lateral to the dentate, the medullary substance was deeply stained. All 3 glial elements were hyperplastic in the dentate nuclei; the Holzer method demonstrated the tangled meshwork of glial fibrils between the folds (Fig. 4B). Dentate nerve cells were noticeably reduced; the few remaining neurons were sparsely scattered in the folds and were deeply stained and shrunken. Interestingly, the Glees silver preparation showed clusters of argyrophilic granules, interpreted as degenerated terminal buttons, around these cells (Fig. 5A). In this same picture, degenerated nerve fibers, some terminating in bulbous swellings, may be observed. The Glees silver preparation also revealed degenerative changes in some of the Purkinje cells, and empty baskets (Fig. 5B). Central cores of folia showed slight or moderate astrocyte proliferation.

In the medulla oblongata, slight loss of nerve cells occurred in the inferior olives and intense gloisis in and between the folds. The dorsal motor nuclei of the vagus nerves also had astrocyte proliferation.

In the upper cervical cord, peripheral zones were pale in lateral and ventral columns and in interfascicular bundles of the dorsal columns. Glial reaction was present only in the central gray matter and ventral horns and was slightly more noticeable on the side that had loss of motoneurons.

Blood vessels in various areas showed slight thickening and hyaline changes or proliferation of their lining cells.

Case 2. A woman between 54 and 64 years old was admitted to St. Elizabeth's Hospital on February 6, 1942. She had had good health until 1913 when diabetes mellitus was diagnosed. However, the disease was well controlled by diet and insulin therapy.

On admission, the patient was weak. For a year she had had progressive gait disturbance and had fallen on several occasions. The patient had difficulty beginning and ending speech—which was slurred and monotonous; her phrases were stereotyped.

At physical examination, the patient could walk only with assistance and had a sidewise and accelerated gait. She had profuse lacrimation of both eyes which was sometimes associated with explosive, guttural sobbing. Blinking was infrequent; both lids had a ptotic tendency. Extraocular movements were extremely slow, and, at times, were accompanied by nystagmoid jerks. Visual fields were grossly normal. Her pupils were round and reacted to light, and she was unable to converge. Her face was expressionless, but she smiled wanly on appropriate stimulation. The movements of her tongue from side to side were slow. She had difficulty in swallowing solid foods and occasionally drooled.

Muscles of the patient's neck and extremities showed marked hypertonicity of the leadpipe variety. Movements of her hands were slow, and her

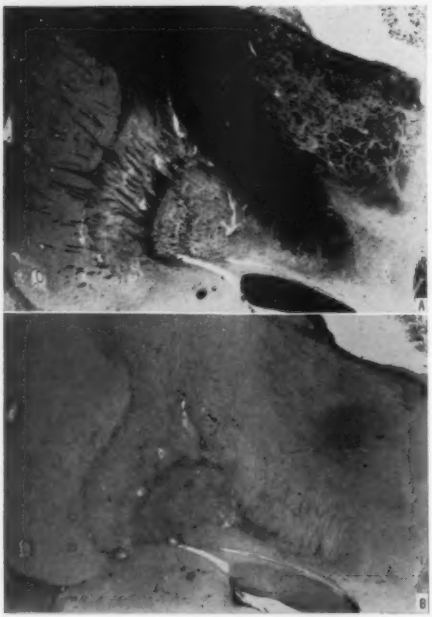

Fig. 6. *Case* 2. (A) Decrease of myelin in globus pallidus and ansa lenticularis. Weil stain. (B) Reactive gliosis, most noticeable in internal segment and medullary laminae of pallidum. Holzer stain

handgrip was weak bilaterally. She did not have tremor. Deep tendon reflexes were active and equal; abdominal reflexes were absent. She had transient Hoffmann's sign on the right and Chaddock's reflex on the left. Her station was rigid; her body and extremities were held in a position of partial flexion. Sensation was intact in all modalities, except for slightly decreased vibratory perception over her feet. She was not mentally abnormal.

By June 1942, the patient was confined to bed or wheel chair, and all her needs had to be cared for. She was often in semistupor; her speech was unintelligible. On December 29, 1943, she was described as weaker, more rigid, unable to swallow solid foods, and accepting liquids poorly. Her temperature rose to 104.6° F. before her death on January 2, 1944.

Laboratory tests showed only slight or no elevation of her blood sugar during her hospitalization until her final illness.

*Necropsy.** The patient's death was attributed to bronchopneumonia and generalized arteriosclerosis. Other findings were not remarkable. The brain weighed 1,080 gm. and gaping of the sulci was noted in frontal and parietal regions. Cerebral arteries were thin-walled. At dissection, slight ventricular dilation was described. The substantia nigra showed pallor. No other changes were observed, and much of the brain was discarded: only the brain stem, cerebellum, and one thick coronal slice through the center of the cerebral hemispheres were saved.

In reviewing old material four years later, I recognized the potential importance of the case. The difficulty in initiating movements was interesting, and sections for histologic study were taken.

The same stains were employed as in the previous case.

At this examination, hypoplasia of the brachium conjunctivum was noted.

At the time of review, sections were taken from the left basal ganglia, the left thalamus, and right and left cerebellum. After preliminary microscopic examination of the pallidum, I wanted to obtain symmetric sections from subcortical structures; unfortunately, the remaining tissues were in such poor condition that further study could not be done. The symmetry of the changes in the brachium conjunctivum, the knowledge that degenerative diseases of the basal ganglia are nearly always symmetric, and the fact that no gross asymmetry was observed are sufficient reasons for believing that the pallidal and thalamic changes were symmetric in this case also.

Microscopic examination of brain. Cortical architecture was poorly maintained, but no apparent loss of nerve cells occurred. Cytolysis and karyolysis were observed, and some of the larger pyramidal cells contained increased lipofuscin.

In the pallidum, efferent fibers were almost completely absent (Fig. 6A). Myelinated tracts of adjacent areas were well stained, including the large bundles of striatum. Few myelinated fibers were found in the hypothalamus and central portion of the thalamus. Almost all nerve cells had disappeared from both segments of the globus pallidus. The few remaining neurons were pale, swollen, and occasionally vacuolated. Holzer stain demonstrated fibrillary gliosis most prominently in the inner segment of the pallidum (Fig. 6B), both medullary laminae, fasciculus subthalamicus, and comb fibers. Many of the hyperplastic astrocytes in both pallidal segments were hypertrophied. Astrocytes were moderately proliferated in the ventral portions of the external and extreme capsules, ventral part of lateral nucleus of the thalamus, stria terminalis, amygdala, and hypothalamus but not in the caudate nucleus or putamen. Nerve cell changes in relatively undamaged areas were not significant. No degenerated terminal buttons were observed in the Glees preparation.

In a level through the arcuate and red nuclei, the paucity of myelin and poor staining reaction of remaining sheaths in the thalamus were striking. The internal medullary lamina was absent. The small size of the nucleus ruber and loss of

*Autopsy was performed twenty-four hours after death by Dr. K. H. Langenstrass.

fibers in and around it were significant. Reactive astrocytosis was most intense in this area and in the substantia nigra. The caudal part of the subthalamic nucleus was present in the sections and also showed gliosis. In the red nucleus, only the large nerve cells were identified. In general, the diencephalic centers appeared to have their normal content of nerve cells, with the possible exception of the centromedian nucleus, which was spongy and had gliosis of its capsule.

In the midbrain, the most prominent feature was the paucity of decussating fibers in the brachium conjunctivum. Some loss of fibers occurred in the tectum and central tegmental tract. Loss of pigmented nerve cells in each locus niger was not significant and was chiefly confined to the central part of the zona compacta. Astrocytes were hyperplastic in each nigra and throughout the tegmentum and tectum; fibrillary gliosis was present in the brachial decussation.

The dystrophy of each brachium conjunctivum was more apparent in the section through the upper pons (Fig. 8B); volume was reduced to one-half the normal. The loss of fibers was almost confined to the medial half bilaterally. One locus cæruleus was intact, but pigmented nerve cells had dropped out of the other. In each, some degenerated myelin sheaths and nerve fibers were identified.

As in the previous case, the dentate nucleus showed diffuse loss of nerve cells which was not restricted to any one area; sometimes a long stretch would be completely devoid of parenchymal elements. The remaining neurons were shrunken and pyknotic. Curiously, again as in Case 1, many of these diseased cells were surrounded by a close network of nerve fibers which terminated in large, silver-stained balls (Fig. 7). Occasionally, a fine reticular structure could be observed in these terminals instead of the club-shaped ending. In the central area bounded by the folds of the dentate, foci of myelin loss, degenerated axis cylinders, and reactive gliosis were found. Moderate glial hyperplasia occurred throughout the medullary substance, even in the cores of some of the folia. Purkinje cells were not significantly decreased, and degenerative changes were not as noticeable as in Case 1.

In the medulla oblongata, marked fibrillary gliosis was observed in the hilus of each inferior olive and astrocyte hyperplasia was seen in the folds, although nerve cells had not noticeably decreased. The gliosis was more intense in the ventral half of each olive. Gliosis occurred in the spinal vestibular nuclei and dorsal motor nuclei of the vagus nerves. A slight loss of nerve cells and reactive gliosis occurred in 1 hypoglossal nucleus.

In the upper cervical cord, some loss of myelin was seen in the dorsal columns and gliosis occurred in the medial portion of each ventral horn.

Case 1. In summary, bilateral degeneration of the globus pallidus occurred with reactive gliosis which was most apparent in the external segments;

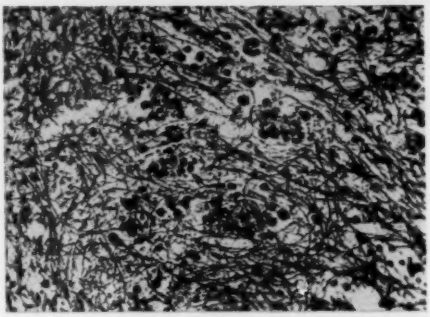

Fig. 7. *Case 2.* Clusters of hypertrophied terminal buttons at sites of dentate nerve cells which have disappeared. (Glees stain, × 600)

atrophy of efferent pallidal pathways, particularly of the fasciculus lenticularis; atrophy and gliosis of the dentate nuclei with degenerated terminal buttons around diseased cells; bilateral atrophy of the brachium conjunctivum; dystrophy of red nuclei with loss of small nerve cells; dystrophy of centromedian nuclei; dystrophy of each locus cæruleus; focal loss of Purkinje cells, with others showing degenerative changes; focal dystrophy in cuneate tracts; focal loss of motoneurons of cervical cord; and focal gliosis of other regions.

Case 2. The chief pathologic changes consisted of significant degeneration of the globus pallidus with extreme reactive gliosis in the internal division and atrophy of the efferent fibers most prominent in the ansa lenticularis; dystrophy of dentate nucleus, brachium conjunctivum, red nucleus, and lateral ventral nucleus of the thalamus; dystrophy and gliosis of substantia nigra, centromedian nucelus, and 1 hypoglossal nucleus; and diffuse astrocytosis or fibrillary gliosis in tegmental areas and reticular substance. Degenerating terminal buttons or nerve fiber endings were unusually large and prominent around damaged dentate cells, although no significant changes were observed in the Purkinje layer.

DISCUSSION

In both patients, the most prominent changes were atrophy of the pallida and their efferent pathways and degeneration of the dentate nuclei and their projection fibers. Thus, apparently a progressive atrophy occurred in 2 components of the extrapyramidal system whose respective influences might be expected to play upon one another in the common meeting ground of thalamus and tegmentum. Since no concomitant atrophy of the dentate nucleus generally occurs in progressive atrophy of the

pallidum, the appearance of the 2 system atrophies in the same individuals might be regarded as fortuitous.

In the literature of physiology[3] and anatomy,[4,5] the term extrapyramidal has been confined to the basal ganglia structures and their projections. Jakob, however, includes the dentatorubral pathways in the extrapyramidal system.[6,7] Hallervorden, too, specifically included the dentate nuclei among the components of the extrapyramidal system.[8] He stated that the nuclei are connected together into neuronal circuits which regulate the motor performances. "The disease syndromes are not related to a single center but always to the whole system."

In the extensive literature pertaining to extrapyramidal disorders, few references are found to differential degeneration of the 2 pallidal divisions. In Papez' discussion of the fiber connections of the basal ganglia,[9] he refers to the difference in origin and topical connections of the 2 divisions and regards them as individual components, although the histologic structure is uniform. He adds that the generalized distribution of the inferior thalamic peduncle to the pallidum and of the pallidal efferent fibers suggests that the function of the globus pallidus is more generalized than specific. On the other hand, the separateness of the striopallidal fiber bundles suggests a topical function. That the blood supply of the 2 segments differs may be significant; the medial receives the distribution from the anterior choroidal artery, the outer from the lenticulostriate branches.

In the reported cases, nerve cell loss was evident in both pallidal divisions, but, in the patient with excessive motor activity, the reactive gliosis was much more intense in the *external* segment; in the rigid patient, the reactive gliosis was much more intense in the *internal* segment. In conformance with the known origin of the efferent paths, the fasciculus lenticularis was almost nonexistent in the first instance and the ansa lenticularis most involved in the second.

Supporting the relationship of the outer pallidal division to involuntary movements was the finding of Jervis and Joyce[10] in a case of barbiturate intoxication followed by choreoathetotic activity. Pathologic study showed bilateral necrosis of the basal ganglia, particularly in the *outer* segment of each pallidum. On the other hand, Holzer[11] reported finding prominent gliosis in the outer segment, in an extremely rigid patient who was diagnosed as a case of "paralysis agitans without agitation." As Holzer pointed out, this differential gliosis is demonstrable only with his technic for glia staining. Klaue[12] could not confirm Holzer's findings in a similar study of 30 patients with typical paralysis agitans. Greenfield[13] remarks that Holzer's case is the only one in his literature review where such functional localization of the pallidum has been proposed.

These observations led to a review of 15 cases of Huntington's chorea which had been autopsied in the previous twenty years. All the autopsies revealed atrophy of the neostriatum with significant reactive astrocytosis. In only the last 4 cases were Holzer preparations available: in all of them, the *external* pallidal divisions showed more intense fibrillary gliosis than the internal, although nerve cells were not significantly decreased in either segment.

Another patient at this hospital was described as being extremely slow in all his movements, with a stiff, stumbling gait which caused him to fall occasionally. He spoke with obvious effort, but the content of his speech was relevant. His face was bilaterally flattened. The chief pathologic findings were bilateral atrophy of the globus pallidus accompanied by degeneration of each ansa and fasciculus lenticularis. Loss of neural elements and reactive gliosis were most prominent in the internal pallidal divisions.

Cases of pure pallidal degeneration described as a syndrome are rare. All have occurred in young persons. In Hunt's discussion of progressive atrophy of the globus pallidus, loss of nerve cells and glial hyperplasia appeared to be uniform.[14] Hunt found no changes in thalamus, red nucleus, substantia nigra, or subthalamic nucleus, although afferent fibers to these centers were atrophic.

In Winkleman's patient,[15] rigidity was first noted at the age of 12. Winkleman stated that all forms of voluntary movements were completely absent; no tremor, chorea, or athetosis. The patient spoke loudly and enunciated with great difficulty. The rigidity became so intense that contractures resulted. Winkleman said

that in the pallidum, neuronal elements disappeared and were replaced by lipoid and iron-containing pigment. The *inner* segment was most severely affected. Alterations in the reticular part of the nigra were similar to those of the pallidum. He pointed out that the rigidity of his patient was first manifested in the lower limbs and was greater there than elsewhere. He correlated this with the extreme glial reaction of the inner segment, thus postulating a somatotopic localization, although he mentioned that divergent symptoms have been reported from lesions in similar locations.

In the patient discussed by Papez, Hertzman, and Rundles,[16] bilateral and sharply localized deficiency of the pallidum and its efferent tracts resulted in spastic athetosis and inability to perform coordinated movements. The caudate nucleus and putamen were described as normal.

Ramsay Hunt also reported a primary atrophy of the dentate system, which, because of clinical manifestations, he called dyssynergia cerebellaris myoclonica.[17] Changes in the spinal cord were those found in Friedreich's ataxia, but Hunt believed this was an accidental association with the degenerative condition of the dentate nuclei. All other cerebellar structures were normal. To other recognized atrophies of the cerebellum, he thus added a fifth.

Since cerebellospinal involvement is not infrequent, the association with myoclonus epilepsy in 4 of Hunt's patients suggested the occurrence of 2 independent nervous disorders in 1 individual. Hunt discussed the fact that the dentate disorder was similar to another system disease: primary atrophy of the efferent pallidal system. The pallidal system, like the dentate, is a common pathway and serves to transmit motor impulses from the corpus striatum. Both systems may be the seat of abiotrophy in the sense of Gowers.

The case discussed by Titica and van Bogaert is similar from clinical and pathologic standpoints[18] to Case 1 of this report. Extreme atrophy was seen in the pallidoluysiian system and degeneration almost as severe occurred in the dentatorubral system. The lesions in the basal ganglia were greatest on the right; cell loss was most prominent in the *external* segment; gliosis occurred in all. Titica and van Bogaert believed their findings bridged the "gap between abiotrophies of the cerebellar system and those of extrapyramidal opticostriate system."

Jakob stated that disturbance of the extrapyramidal type may be found in cases characterized by lesions of the dentatorubral tract.[6] He concluded that, "the extrapyramid system is built up as a whole on the coordinating mechanism of brainstem and cerebellum."

Onset of symptomatology is gradual in these abiotrophic diseases, and progression is inexorable, involving first one limb and then spreading to all extremities. This slow extension from one part of the body to another certainly suggests somatotopic localization.

In the patients discussed here, the greater gliosis in the external segment in the patient with choreoathetoid movements is probably related to nerve cell damage in the putamen, particularly the large elements. In the rigid patient, nigral changes were more prominent, and a closer relationship of this structure with the internal division is indicated. These findings strongly suggest that the external segment of the pallidum and its connections are concerned with movement, and the internal segment and its associated areas with inhibition of movement or rigidity.

The dissimilar degenerations observed in the brachia conjunctiva also suggest a somatotopic functional activity of the dentate nucleus. That a difference exists in the distribution of degenerative changes in the dentate nuclei of the 2 reported cases is deduced from the location of demyelination in the brachium in the walls of the fourth ventricle (Figs. 8A and B). In Case 1, myelin loss was diffuse, while, in Case 2, the atrophy was strictly confined to each medial portion.

A curious feature was the marked terminal degeneration observed in the dentate nuclei of each patient, particularly in Case 2. These clusters of giant bulbs appear to surround dead or diseased dentate nerve cells. The dentate nucleus is said to derive its entire afferent inflow from the Purkinje cells, which showed slight, if any, change in the areas examined in Case 2. Could this then be an instance of transynaptic degeneration? In Case 1, the terminal buttons were not greatly hypertrophied but the Purkinje cells were frequently in degenerative states and focally had

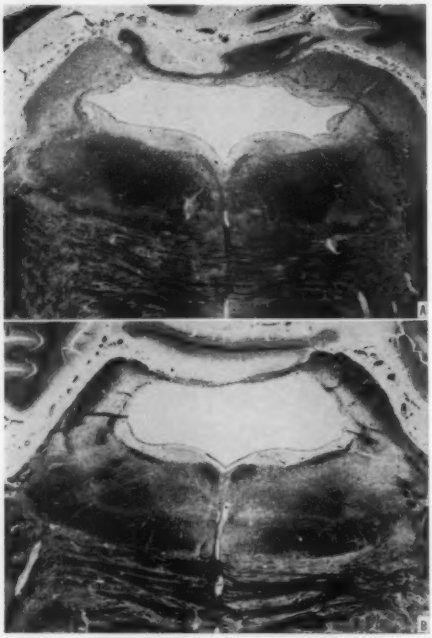

Fig. 8. Distribution of myelin loss in brachium conjunctivum. Weil stain. (A) *Case 1.* Loss of myelin is diffuse. (B) *Case 2.* Loss of myelin is confined to medial parts of brachium conjunctivum.

dropped out, leaving empty baskets. However, the loss of Purkinje cells was in no way comparable to the loss of dentate cells.

In recent years, physiologic experiments[19] have helped elucidate some of the functions and connections of the reticular substance of the brain stem and thalamus. Anatomic and pathologic studies have shown that the pallidum sends fibers to these areas and that the brachium conjunctivum gives off collaterals at various levels of the reticular substance.[9,20,21] The function or role of such connections can only be speculated upon in the present state of our knowledge. Magoun[19] implies that extrapyramidal symptoms are due to failure of reticulospinal fibers to function adequately, but this may be due to loss of proper stimuli from diseased pallidal and dentate inflow.

Apparently, the combinations of areas involved in extrapyramidal disorders are as legion as those encountered in the cerebellar system diseases[22] which seldom involve the dentatorubral-thalamic pathway. Apparently, spatial distribution of lesions within these connected structures critically determines the clinical phenomena. Somatotopic localization is suggested but cannot yet be proved.

ACKNOWLEDGMENTS

The neurologic discussions in this study benefited from the advice of, and from frequent consultations with, Dr. Robert Cohn of the U. S. Naval Hospital, Bethesda, Md., who saw both of these patients shortly after their admission to St. Elizabeths Hospital.

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Neurology

BOOK REVIEWS

Understanding Aphasia: A Guide for Family and Friends

by Martha L. Taylor, 48 pp., The Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center, New York City, 1958. 50 cents

This is an excellent booklet for the family and friends of aphasic patients. Written in simple language, its purpose is to promote understanding of the aphasic patient so that his family can help him in his rehabilitation.

The technic employed in the booklet is that of asking questions which relatives commonly ask and then answering these questions simply and clearly. Interesting illustrations supplement the written text. The book is recommended to the attention of physicians and others interested in the care of aphasic patients.

J. R. B.

Medulloblastoma

by Benjamin L. Crue, 206 pp., Publication Number 339, American Lecture Series, Charles C Thomas, Springfield, Ill. $5.75.

The medulloblastoma has characteristics that make it unique in any classification of cerebral neoplasms. Early in his medical career, the author of this book was intrigued by the problems it suggested and, throughout his neurosurgical training in the various centers where he studied, accumulated data on this tumor. The result is a well documented and thought-provoking monograph.

After a brief introductory discourse on neoplasia in general, the pathologic aspects of the medulloblastomas and related tumors are discussed. Neuropathologists may not agree that the medulloblast has potentialities of producing a neuroblastoma, medulloblastoma, sarcoma, or oligodendroglioma as the author suggests. Perhaps the superficial resemblances of these tumors may be due to factors other than biologic propinquity.

Whether a regrouping of these tumors into one class on the basis of morphology is justified would certainly be questioned by the disciples of Rio del Hortega. The argumentation would have been more convincing in the reviewer's opinion had evidence from metallic impregnations, tissue culture, and heterogenous transplants given presumptive proof of a common origin of these tumors.

In the second half of this monograph, the clinical aspects of cerebellar medulloblastomas are presented. In this review a number of important points concerning age and sex incidence as well as symptomatology are discussed. The treatment of the tumor is critically assessed, comment being made on both the surgical attack and the ionic forms of therapy.

The author points out that, in spite of advances, cure of a medulloblastoma is not yet possible and that a somewhat longer survival is about all that might be expected from even the most elaborate forms of therapy now available.

This little monograph is a well written and easily read critical review of one of the most intriguing brain tumors. It deserves the attention of all interested in the current diagnosis and treatment of cerebral neoplasms.

A. E. W.

Temporal Lobe Epilepsy

edited by Maitland Baldwin and Pearce Bailey, 581 pp. Charles C Thomas, Springfield, Ill., 1958. $15.50.

In March 1957, the Second International Colloquium on Temporal Lobe Epilepsy was held at the National Institutes of Neurological Diseases and Blindness under the auspices of the International League Against Epilepsy. This colloquium was planned to answer some of the questions raised at the first colloquium held in Marseille in 1954.

It is impossible to abstract the material presented in this three day meeting, which was designed to cover anatomicophysiologic and pathologic aspects as well as the surgical therapy and its aftermath of temporal lobe epilepsy. Participating in the presentations and discussions were scientists from neurologic clinics of several European countries, South America, Canada, and the United States. Thus the views of the major centers of the world interested in this problem were represented. It is of little wonder, then, that this colloquium presents the most complete survey of the subject, with perhaps the exception of the clinical aspects, available at this time. Much of the pathologic and surgical material is not available elsewhere.

In spite of the great interest in this subject by neurologists, neurophysiologists, electroencephalographers, and neurosurgeons, few of the problems inherent in the epilepsies of the temporal lobe have been solved. In the first place, there is no agreement upon the anatomic site of origin of such fits or upon the clinical differentiation of cortical and subcortical seizures. Whether the pathologic changes seen in the various temporal lobe structures are the result or cause of the epilepsy has not been proved to the satisfaction of all neuropathologists. The value of the electroencephalographic findings in prognosticating the results of surgical therapy is variously assessed. And finally there is not much agreement upon which anatomic structure or structures should be removed surgically when medical management fails to control the seizures.

This well edited account of the colloquium should be read by all interested in neurologic sciences—the neurologist, neurosurgeon, neurophysiologist, neuroanatomist, psychiatrist, psychologist, or just inquiring scientist.

A. E. W.

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NEWSLETTER

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JUNE 1959

New York Neurological Celebrates Its Fiftieth Anniversary

The Neurological Institute of New York, the first hospital in the Western Hemisphere specifically organized for the medical and surgical treatment of neurological disorders, celebrated its Fiftieth Anniversary at the Columbia-Presbyterian Medical Center in New York, May 15 and 16, 1959. The jubilee program highlighted a scientific program on Friday, May 15; a gala banquet held in the Sert Room of the Waldorf-Astoria Hotel on the same evening; and a convocation on May 16, Columbia University with the Presbyterian Hospital, for the award of honorary degrees, where Byron Stookey and Henry Alsop Riley were presented the degrees of D.Sc. by Columbia University President, Grayson Kirk. H. Houston Merritt, Dean of the Faculty of Medicine, College of Physicians and Surgeons, and Director of the Neurology Service, and J. Lawrence Pool, Professor of Neurological Surgery, presided at the scientific presentations. The speakers included Byron Stookey, "What is Past is Prologue"; Charles M. Pomerat, "The Behavior of Dorsal Root Ganglia in Vitro"; Sir Francis M. R. Walshe, "The Present and Future of Clinical Neurology"; Henry A. Riley, "The Intermediate Years"; Wilder Penfield, "Retrospect and Prospect in Neurosurgery"; and Pearce Bailey, "Neurological Research and Education in the United States." In addition, there was an exhibition of early New York neurologic surgical contributions....The banquet address, "The Future of Man in the Atomic Age," was given by William L. Lawrence, Science Editor of the New York Times....To honor the Institute's anniversary, a series of special events had been held in advance of the anniversary celebration: a joint meeting (March 10) of the New York Neurological Society and the Section of Neurology and Psychiatry of the Academy of Medicine to honor the occasion; the fiftieth annual meeting of the Society of Neurological Surgeons, the senior neurosurgical society in America, held especially at the Neurological Institute of New York to honor its half-century anniversary....The Neurological Institute of New York was founded in 1909 by Doctors Joseph Collins, Pearce Bailey, Sr., and Joseph Fraenkel. It was located at 149-151 East 67th Street until 1929, when it became affiliated with the Columbia-Presbyterian Medical Center.

Neurology Chair Established at Hebrew University

Morris B. Bender reports that a chair in neurology has been created in honor of Dr. I. S. Wechsler at the Hebrew University Medical School in Jerusalem. Dr. Wechsler was formerly

Professor of Clinical Neurology at Columbia University, chief of the Neurologic Service at the Mount Sinai Hospital of New York, and President of the American Neurological Association (1957). The new professorship is called the Israel S. Wechsler Chair in Neurology.

New Training Program in Neuroanatomy at Seton Hall The Seton Hall College of Medicine and Dentistry announces the inauguration of a postdoctoral training program in neuroanatomy, supported in part by the National Institute of Neurological Diseases and Blindness. The neuroanatomy training is correlated with other branches of study of the nervous system and with the general field of anatomy. The curriculum provides training in histology, histochemistry, and biochemistry of neural tissue and muscle; uses of stereotaxic devices; electrophysiologic recording; applications of experimental degeneration methods; studies of genetic mutations with neurologic and myologic defects; and analyses of sensory and motor systems. Candidates holding the M.D. or Ph.D. degree are eligible. Fellowships are awarded for one year and are renewable. Stipends depend on need and qualifications....Inquiries should be directed to the Program Director, Pinckney J. Harman, Ph.D., Department of Anatomy, Seton Hall College of Medicine and Dentistry, 24 Baldwin Avenue, Jersey City 4, N.J.

Research Fellowships and Scholarships of the MS Society Thomas L. Willmon, Medical and Research Director of the National Multiple Sclerosis Society, announces that a limited number of the Society's postdoctoral (M.D. or Ph.D.) fellowships and scholarships are available. The purpose of these appointments, which are renewable annually and may extend to three years, is to foster postgraduate training in studies related to the demyelinating diseases. The stipends are geared to the financial needs of the applicant and to his level of training and experience. The applicant may elect his sponsoring institution. Additional information may be obtained from Dr. Willmon at the National Multiple Sclerosis Society, 257 Fourth Avenue, New York City 10.

Prof. Vogt Receives Distinguished Service Cross Walter L. Bruetsch reports that Prof. Dr. Oskar Vogt, on the occasion of his 89th birthday, was awarded the Distinguished Service Cross, the highest civilian German award. The award was made by the President of the Federal Republic of West Germany in a ceremony at the Neustadt Brain Research Institute in the Black Forest. The Neustadt Institute was founded by Oscar Vogt and his French-born wife, Dr. Cécile Vogt, when the former relinquished the chair of neurology at the University of Berlin

(1934)....Prof. Vogt holds nine honorary doctorates and, together with Max Nonne (Hamburg) and O. Foerster (Breslau), was called as a consultant to Lenin when he suffered a stroke.

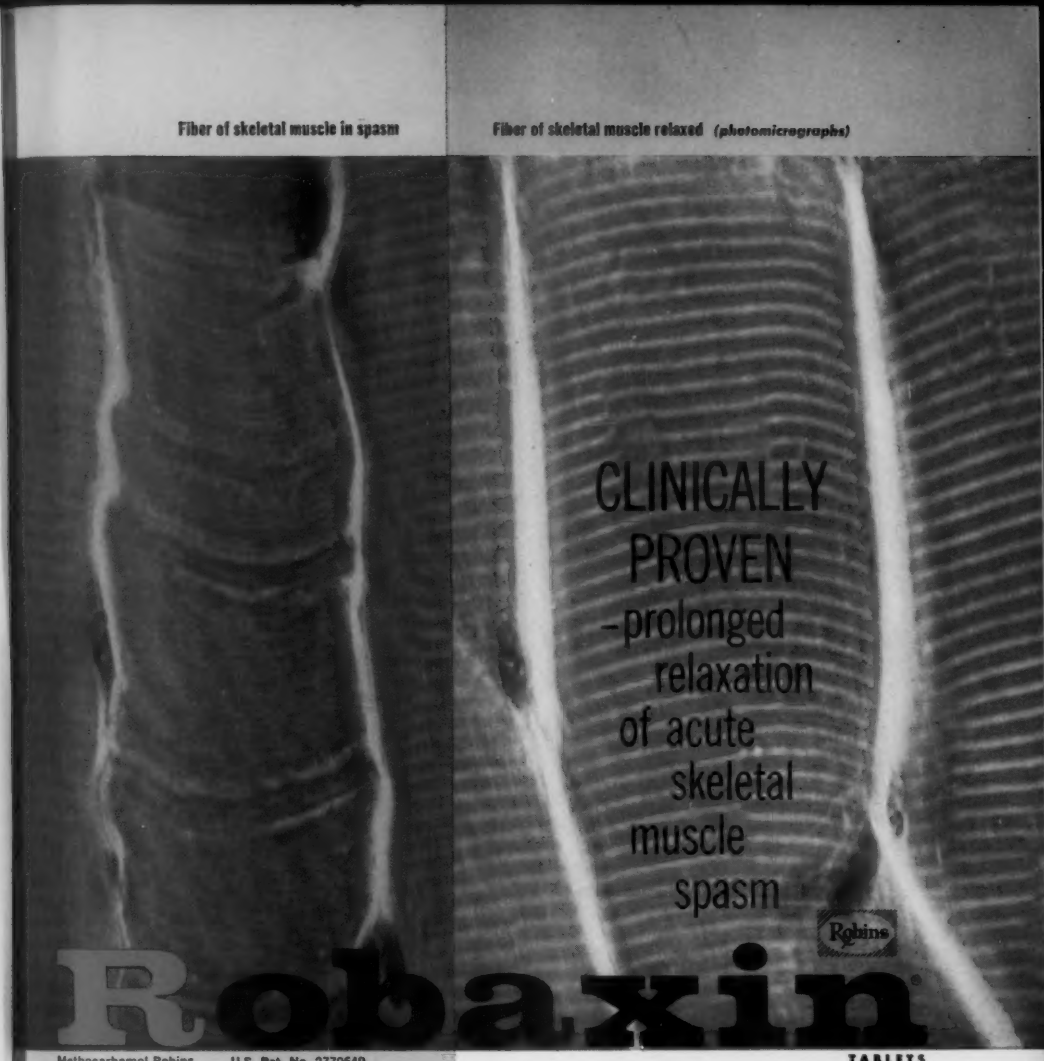
International Conference on Mental Retardation The First International Medical Conference on Mental Retardation will be held July 27-31, 1959, at the Eastland Hotel in Portland, Me. The General Chairman is Dr. Peter W. Bowman of Pownal, Me. All communications should be addressed to the Conference Secretary, c/o Division of Maternal and Child Health, State House, Augusta, Me.

Encephalitis Symposium Held in Antwerp On Monday, May 11, over 50 neurologists and neurological scientists convened in Antwerp from 14 different countries to discuss the neuropathology and pathophysiology of the various encephalitides occurring throughout the world. Organized by Dr. Ludo van Bogaert, President of the World Federation of Neurology and Director of the Institut Bunge in Antwerp, the symposium was sponsored by the Centre Interuniversitaire de Recherches Neuropathologiques in collaboration with the World Federation of Neurology and the National Institute of Neurological Diseases and Blindness. Among the countries represented were Austria, Belgium, Czechoslovakia, Denmark, France, Germany, Great Britain, Hungary, Italy, Netherlands, Poland, Romania, Switzerland, and the United States. Among the participants from the United States were: Albert B. Sabin, A. B. Baker, D. Carleton Gajdusek, Igor Klatzo, and Webb Haymaker.... The scientific sessions were opened on the morning of May 11, by Dr. van Bogaert with discussions on the arthropod-borne encephalitides, Eastern equine encephalomyelitis, rabies encephalitis, herpetic encephalitis, and encephalitis associated with Asiatic "flu." The afternoon program of the same day was devoted to post-vaccinal encephalitis and to encephalitis associated with neoplasms. These sessions ended with a demonstration of "Kuru" disease by Gajdusek and Klatzo. The next day, May 12, the discussions centered on encephalitis and granulomas and on the acute necrotic encephalitides. The morning sessions of the 13th concerned principally the consideration of the subacute sclerosing leukoencephalitides (Dawson, Pette-Döring, and van Bogaert). On the afternoon of the same day there was a discussion of the classification of the atypical encephalitides of unknown etiology. These discussions on the neuropathology and classification of the encephalitides were summarized by Haymaker (U.S.A.), Jacob (Germany), and van Bogaert (Belgium)....On the morning and afternoon of Thursday, May 14, the neuropathologic symposium was followed by demonstrations and discussions of the EEG tracings in encephalitis (J. Radermecker, Chairman); the biology and biochemistry of the encephalitides (Dr. Lowenthal, Chairman), including discussions of electrophoretic studies of the blood serum and cerebrospinal fluid, antibodies in

the encephalitides, and the neurochemistry of the encephalitides. The conferees in the neurochemical sessions included Bauer (Germany), Cummings (Great Britain), Edgar (Netherlands), and Karcher (Belgium)....The transactions of the Antwerp Symposium will be published as a monograph.

Yakovlev Seeks Autopsy Material Paul I. Yakovlev and Edward P. Richardson of the Warren Anatomical Museum of the Harvard Medical School are studying the standard criteria of the normal myelination process of the human nervous system from birth to puberty. They wish to establish comparative age gradients of normal myelination for comparison with the retarded and pathological myelination, employing routine histological technics for staining myelin. Since a statistically sufficient amount of autopsy material of reasonably normal brains and spinal cords of human infants and children in this age group is difficult to collect from any single geographic area, Yakovlev and Richardson are appealing to departments of pathology and to medical institutions that are authorized to perform autopsies to send them as much of this material as they can spare for this study....For this study, the specimens of cerebra of infants and children should be reasonably free from disease. They should be removed whole with the brain stem and cerebellum and should be perfused immediately after removal with 200 to 300 cc. of 4 to 10% formalin solution through the internal carotid and vertebral arteries. The perfused specimens should be suspended in at least 10 times their volumes of formalin for a few days to two weeks. When fixed, they should be placed in a cellophane bag and packed with ordinary Vaseline in a tin can of suitable size. The tin cans and packing material will be supplied on request. The sealed tin can with the specimen and information on it should be sent by railway express, C.O.D., to: Myelination Laboratory; Warren Anatomical Museum; 25 Shattuck Street; Boston 15. Specimens so received will be prepared in gapless serial whole-brain celloidin sections. The senders of each pertinent specimen will be supplied with a complete set of unstained sections at intervals of every twentieth section through the entire specimen. Unsuitable specimens will be returned to the sender at the Laboratory's cost. All expenses entailed in preparing, packing, and shipping the specimens will be met by the Myelination Laboratory.

Percy Bailey



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Forsyth[2]	58	37	20	—	1
		"good"			
Lewis[3]	38	25	6	—	7
O'Doherty & Shields[4]	17	"excellent" 14	2	1	0
		"significant"			
Park[5]	30	27	—	2	1
		"gratifying"			
Plumb[6]	60	55	—	—	5
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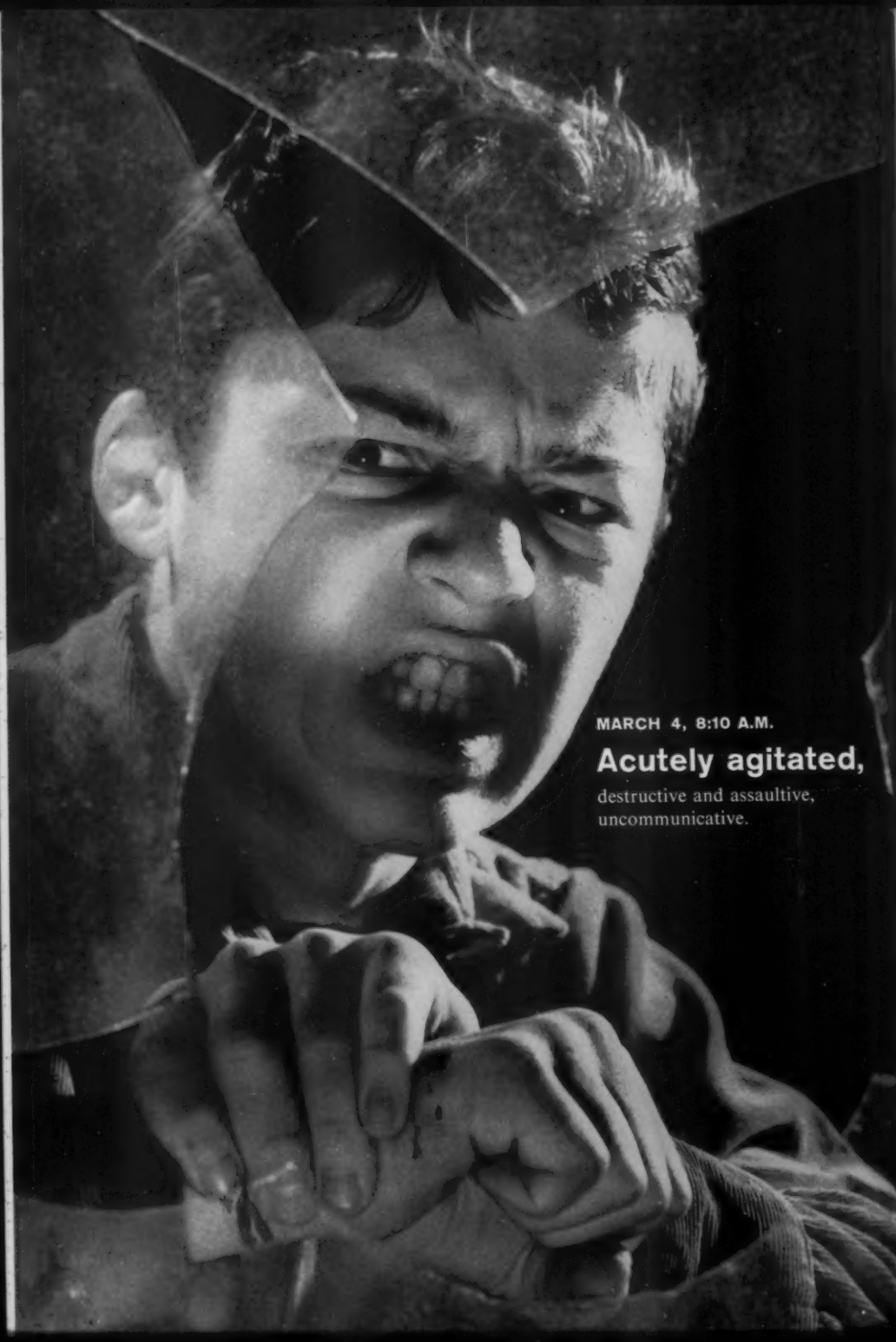
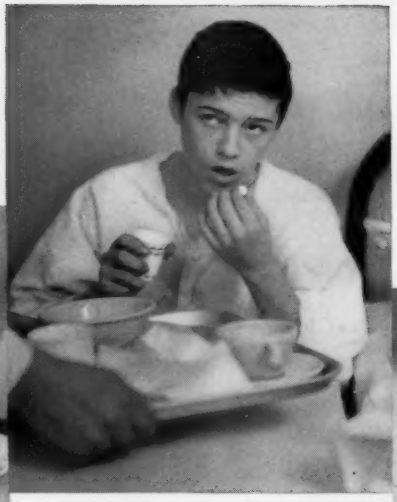

MARCH 4, 8:10 A.M.
Acutely agitated,
destructive and assaultive,
uncommunicative.

RCH 4, 10:00 A.M.
RINE, I.V., has been given.
ent in light sleep.
be awakened readily,
responds to questioning.



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about smashed window.

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